

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 November 2002 (21.11.2002)

PCT

(10) International Publication Number
WO 02/092585 A1

(51) International Patent Classification⁷: C07D 295/04, 241/04, 211/46, 233/56, 243/08, 215/36, 453/02, 487/04, 487/08, A61K 31/495, 31/551, 31/4164, 31/445, 31/439, 31/496, A61P 3/04, C07D 487/08, A61K 31/495, 31/551, 31/4164, 31/445, 31/439, 31/496, A61P 3/04

(21) International Application Number: PCT/SE02/00906

(22) International Filing Date: 8 May 2002 (08.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|------------|--------------------------|----|
| 0101659-1 | 11 May 2001 (11.05.2001) | SE |
| 0101660-9 | 11 May 2001 (11.05.2001) | SE |
| 60/294,132 | 29 May 2001 (29.05.2001) | US |
| 60/294,102 | 29 May 2001 (29.05.2001) | US |
| 0101958-7 | 5 June 2001 (05.06.2001) | SE |

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Declaration under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR)

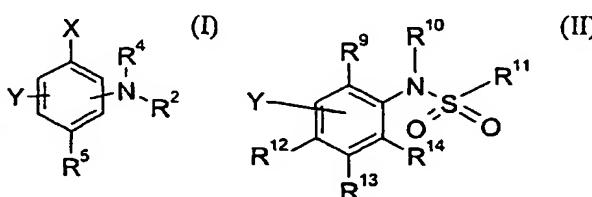
Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/092585 A1

(54) Title: NOVEL, ARYLSUSFONAMIDE COMPOUNDS FOR THE TREATMENT OF OBESITY, TYPE II DIABETES AND CNS-DISORDERS



(57) Abstract: The present invention relates to substituted bis-arylsulfonamide and arylsulfonamide compounds of the general formula (I) or the formula (II), which compounds are potentially useful for the prophylaxis and treatment of medical conditions relating to obesity, type II diabetes and/or disorders of the central nervous system.

**NOVEL, ARYLSULFONAMIDE COMPOUNDS FOR THE TREATMENT OF OBESITY, TYPE II
DIABETES AND CNS-DISORDERS**

RELATED APPLICATIONS

This application claims priority to Swedish application number 0101660-9, filed on
5 May 11, 2001, U.S. provisional application number 60/294,102, filed on May 29, 2001, and
U.S. provisional application number 60/294,132, filed on May 29, 2001, the contents of
which are incorporated herein by reference.

TECHNICAL FIELD

10

The present invention relates to substituted bis-arylsulfonamide and arylsulfonamide
compounds, to pharmaceutical compositions comprising these compounds, and to the use of
the compounds for the prophylaxis and treatment of medical conditions relating to obesity,
type II diabetes and/or disorders of the central nervous system.

15

BACKGROUND ART

Obesity is a condition characterized by an increase in body fat content resulting in
excess body weight above accepted norms. Obesity is the most important nutritional disorder
20 in the western world and represents a major health problem in all industrialized countries.
This disorder leads to increased mortality due to increased incidences of diseases such as
cardiovascular disease, digestive disease, respiratory disease, cancer and type II diabetes.
Searching for compounds, which reduce body weight has been going on for many decades.
One line of research has been activation of serotonergic systems, either by direct activation
25 of serotonin receptor subtypes or by inhibiting serotonin reuptake. The exact receptor
subtype profile required is however not known.

Serotonin (5-hydroxytryptamine or 5-HT), a key transmitter of the peripheral and
central nervous system, modulates a wide range of physiological and pathological functions,
including anxiety, sleep regulation, aggression, feeding and depression. Multiple serotonin
30 receptor subtypes have been identified and cloned. One of these, the 5-HT₆ receptor, was

cloned by several groups in 1993 (Ruat, M. et al. (1993) *Biochem. Biophys. Res. Commun.* 193: 268-276; Sebben, M. et al. (1994) *NeuroReport* 5: 2553-2557). This receptor is positively coupled to adenylyl cyclase and displays affinity for antidepressants such as clozapine. Recently, the effect of 5-HT₆ antagonist and 5-HT₆ antisense oligonucleotides to 5 reduce food intake in rats has been reported (Bentley, J.C. et al. (1999) *Br J Pharmac. Suppl.* 126, P66; Bentley, J.C. et al. (1997) *J. Psychopharmacol. Suppl.* A64, 255).

Compounds with enhanced affinity and selectivity for the 5-HT₆ receptor have been identified, e.g. in WO 00/34242 and by Isaac, M. et al. (2000) *6-Bicyclopiperazinyl-1-arylsulfonylindoles and 6-Bicyclopiperidinyl-1-arylsulfonylindoles derivatives as novel, potent and selective 5-HT₆ receptor antagonists*. *Bioorganic & Medicinal Chemistry Letters* 10: 1719-1721.

DISCLOSURE OF THE INVENTION

15 It has surprisingly been found that the compounds of formula (I) and (II) show affinity for the 5-HT₆ receptor as antagonists at a low nanomolar range. Compounds according to the invention and their pharmaceutically acceptable salts have 5-HT₆ receptor antagonist activity and are believed to be of potential use in the treatment or prophylaxis of obesity and type II diabetes, as well as in the treatment or prophylaxis of disorders of the 20 central nervous system such as anxiety, depression, panic attacks, memory disorders, sleep disorders, binge disorders, migraine, anorexia, bulimia, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea and/or schizophrenia, drug abuse, Attention Deficit Hyperactive Disorders (ADHD).

25 *Definitions*

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and the appended claims:

The term "C₁₋₆ alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said lower alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

5 The term "C₁₋₆ alkoxy" denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said lower alkoxy include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight- and branched-chain pentoxy and hexoxy.

10 The term "halogen" shall mean fluorine, chlorine, bromine or iodine.

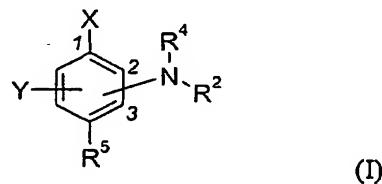
The terms "C₄₋₆ cycloalkyl" and "C₃₋₇ cycloalkyl" denote a cyclic alkyl group having a ring size from C₄ to C₆ or from C₃ to C₇, respectively. Examples of said cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl and cycloheptyl.

15

Compounds of Formula I

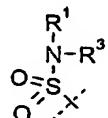
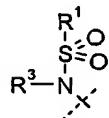
In a first aspect, this invention provides a compound of the general formula (I)

20



or a pharmaceutically acceptable salt thereof, wherein

X is



25

R^1 and R^3 are independently

- (a) H
- (b) C_{1-6} alkyl,
- (c) C_{1-6} alkoxy,
- 5 (d) straight or branched C_{1-6} hydroxyalkyl,
- (e) straight or branched C_{1-6} alkylhalides; or
- (f) a group Ar;

Ar is

- 10 (a) phenyl,
- (b) 1-naphthyl,
- (c) 2-naphthyl,
- (d) benzyl,
- (e) cinnamoyl,
- 15 (f) a 5 to 7-membered, partially or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur, or
- (g) a bicyclic ring system consisting of two heterocyclic rings as defined under (f), or a bicyclic ring system consisting of one benzene ring and one heterocyclic ring as defined under (f);
- 20 alternatively, R^1 and R^3 are linked to form a group $(CH_2)_2O$, $(CH_2)_4O$, or $(CH_2)_{3-5}$ in formula (Ib);

optionally, the group Ar is substituted with

- 25 (a) Y, or
- (b) a 5 to 7-membered, partially or completely saturated, heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

Y is

- 30 (a) H,
- (b) halogen,

- (c) C₁₋₆ alkyl,
- (d) CF₃,
- (e) hydroxy,
- (f) C₁₋₆ alkoxy,
- 5 (g) C₁₋₄ alkenyl;
- (h) phenyl;
- (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- 10 (l) OCF₃,
- (m) CN,
- (n) straight or branched C₁₋₆ hydroxyalkyl,
- (o) straight or branched C₁₋₆ alkylhalides,
- (p) NH₂,
- 15 (q) NHR⁶,
- (r) NR⁶R⁷,
- (s) NO₂,
- (t) -CONR⁶R⁷,
- (u) NHSO₂R⁶,
- 20 (v) NR⁶COR⁷,
- (x) SO₂NR⁶R⁷,
- (z) -C(=O)R⁶,
- (aa) -CO₂R⁶, or
- (ab) S(O)_nR⁶; wherein n is 0, 1, 2 or 3;

25

R² and R⁴ are independently:

- (a) -SO₂R¹,
- (b) H,
- (c) C₁₋₆ alkyl,
- 30 (d) C_{1-C₃} alkenyl,
- (e) C_{1-C₃} alkylaryl,

(f) Ar as defined above for R¹,

(g) -C(=O)R⁶,

(h) -C(O)NR⁶R⁷,

(i) -C(S)NR⁶R⁷,

5 (j) -CO₂R⁶;

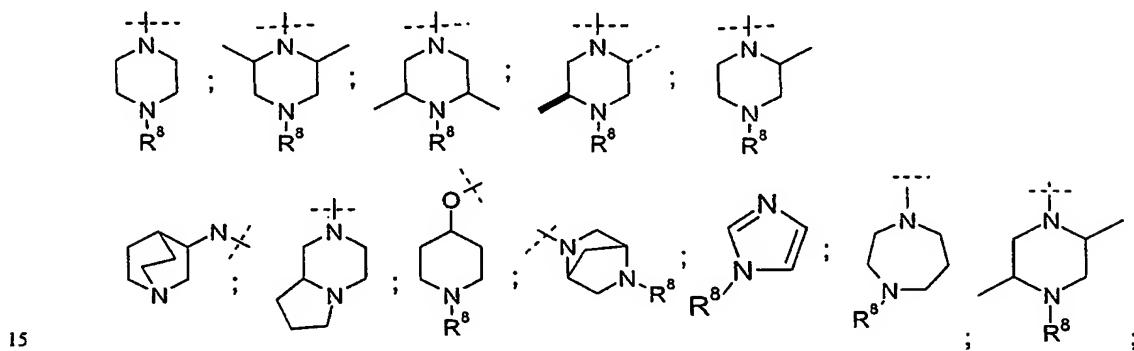
(k) -C(S)R⁶;

(l) straight or branched C₁₋₆ hydroxyalkyl, or

(m) straight or branched C₁₋₆ alkylhalides;

10 alternatively, R² and R⁴ are linked to form a group (CH₂)₂O, (CH₂)₄O, or (CH₂)₃₋₅ in formula (Ia);

R^5 is selected from the group consisting of the following chemical groups:



R^6 and R^7 are independently

(a) H,
 (b) C_{1-6} alkyl,
 20 (c) C_{3-7} cycloalkyl, or
 (d) Ar, as defined above in R^1 ;

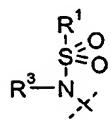
alternatively, R⁶ and R⁷ are linked to form a group (CH₂)₂O, (CH₂)₄O or (CH₂)₃-5;

R^8 is

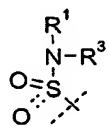
- (a) H, or
- (b) C_{1-6} alkyl.

5 Preferred compounds of the general formula (I) are those wherein:

X is



(Ia)



(Ib)

10

R^1 is

- (e) a group Ar; or
- (f) C_{1-6} alkyl

15

Ar is

- (a) phenyl,
- (b) 1-naphthyl,
- (c) 2-naphthyl, or

20 (f) a 5 to 7-membered, partially or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur;

the group Ar is substituted with Y, wherein Y is

- (a) H,
- (b) halogen,
- (c) C_{1-6} alkyl,
- (d) CF_3 ,
- (f) C_{1-6} alkoxy,

- (g) C₁₋₄ alkenyl;
- (h) phenyl;
- (i) OCF₃, or
- (n) straight or branched C₁₋₆ hydroxyalkyl;

5

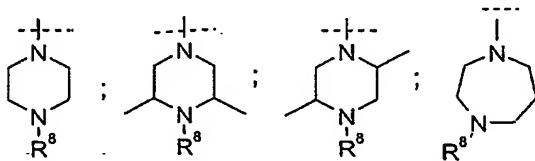
the group $\begin{array}{c} \text{R}^4 \\ | \\ -\text{N}-\text{R}^2 \end{array}$ is attached to the phenyl ring in 2-position or in 3-position;

R² and R⁴ are independently

- (a) H
- 10 (b) C₁₋₃ alkyl, in particular methyl or ethyl
- (c) -SO₂R¹; or
- (d) are linked to form a group (CH₂)₄O

R⁵ is selected from the group consisting of the following chemical groups:

15



wherein R⁸ is

- (a) H, or
- 20 (b) C₁₋₆ alkyl, in particular methyl.

R⁶ and R⁷ are independently

- (a) H,
- (b) C₁₋₆ alkyl,
- 25 (c) C₃₋₇ cycloalkyl, or
- (d) Ar.

N-[2-[ethyl(phenylsulfonyl)amino]-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

3-fluoro-N-[2-[(3-fluorophenyl)sulfonyl]amino]-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

5 N-{4-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride

4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

10 N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide hydrochloride

15 2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

4-butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

20 5-fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

2-methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride

25 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{5-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-N-ethylbenzenesulfonamide hydrochloride

30 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride

5 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,4,6-trimethylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride

10 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-fluoro-2-methylbenzenesulfonamide hydrochloride

N-{5-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

15 3-amino-4-(1,4-diazepan-1-yl)-N-(2-methoxyphenyl)benzenesulfonamide hydrochloride

3-amino-N-(3-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide hydrochloride

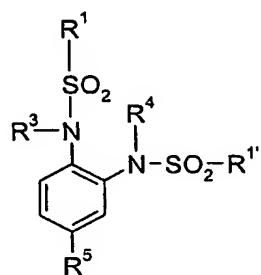
3-amino-N-(2-methoxyphenyl)-4-(1-piperazinyl)benzenesulfonamide hydrochloride

20 2-[1,4]Diazepan-1-yl-5-(3,4-dihydro-1H-isoquinoline-2-sulfonyl)-aniline dihydrochloride

hydrochloride

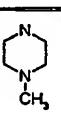
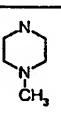
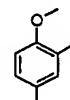
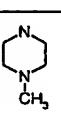
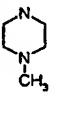
3-Amino-2-chloro-N-naphthalen-1-yl-4-piperazin-1-yl-benzenesulfonamide, hydrochloride hydrochloride

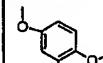
TABLE I

Compounds of the formula I wherein R² is -SO₂-R^{1'}

5

| | Name | R ¹ | R ^{1'} | R ³ | R ⁴ | R ⁵ |
|---|---|----------------|-----------------|----------------|----------------|----------------|
| 1 | N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide | | | H | Et | |
| 2 | N-[2-{ethyl(phenylsulfonyl)amino}-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide | | | H | Et | |
| 3 | 3-fluoro-N-[2-{[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]benzenesulfonamide | | | H | H | |
| 4 | N-{4-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride | | | H | H | |
| 5 | N-[2-chloro-4-({4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]anilino}sulfonyl)phenyl]acetamide | | | H | H | |
| 6 | 3,4-dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide | | | H | H | |

| | Name | R ¹ | R ^{1'} | R ³ | R ⁴ | R ⁵ |
|----|---|---|---|----------------|----------------|---|
| 7 | 3-methoxy-4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide |  |  | H | H |  |
| 8 | 4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide |  | -CH ₃ | H | H |  |
| 9 | 3,4-dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide |  | -CH ₃ | H | H |  |
| 10 | 3-cyano-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide |  | -CH ₃ | H | H |  |
| 11 | N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide |  |  | H | H |  |
| 12 | 5-(dimethylamino)-N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide |  |  | H | H |  |
| 13 | N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide |  |  | H | H |  |
| 14 | 2,4,6-trimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 15 | 4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 16 | N-[2-({(E)-2-phenylethethylsulfonyl}amino)-5-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |

| | Name | R ¹ | R ^{1'} | R ³ | R ⁴ | R ⁵ |
|----|--|---|---|----------------|----------------|---|
| 17 | 2,5-dimethoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 18 | 2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 19 | 2,4-difluoro-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 20 | 4-butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 21 | 3,5-dimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-4-isoxazolesulfonamide |  |  | H | H |  |
| 22 | 5-fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 23 | 4-(methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 24 | 2-(methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 25 | 2-methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |
| 26 | 4-methoxy-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide |  |  | H | H |  |

| | | | | | | |
|----|---|--|---|---|----|---|
| 27 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide |  |  | H | H |  |
| 28 | N-(4-(1,4-diazepan-1-yl)-2-[(3-fluorophenyl)sulfonyl]amino)phenyl)-3-fluorobenzenesulfonamide |  |  | H | H |  |
| 29 | N-{5-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-N-ethylbenzenesulfonamide |  |  | H | Et |  |
| 30 | N-(5-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl)benzenesulfonamide | Me |  | H | H |  |
| 31 | N-(5-(1,4-diazepan-1-yl)-2-[(ethylsulfonyl)amino]phenyl)benzenesulfonamide | Et |  | H | H |  |
| 32 | N-(4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl)[1,1'-biphenyl]-4-sulfonamide |  |  | H | H |  |
| 33 | N-(4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl)-2,1,3-benzoxadiazole-4-sulfonamide |  |  | H | H |  |
| 34 | N-(4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl)-2-naphthalenesulfonamide |  |  | H | H |  |
| 35 | N-(4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl)benzenesulfonamide |  | Me | H | H |  |
| 36 | N-(4-(1,4-diazepan-1-yl)-2-[(methyl(methylsulfonyl)amino)phenyl]benzenesulfonamide PHA-526210A |  | Me | H | Me |  |

| | | | | | | |
|----|--|---|---|----|----|---|
| 37 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide |  | Me | Me | H |  |
| 38 | N-{4-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}benzenesulfonamide |  |  | H | Me |  |
| 39 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide |  | Me | H | H |  |
| 40 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide |  | Me | H | H |  |
| 41 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-fluorobenzenesulfonamide |  | Me | H | H |  |
| 42 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-nitrobenzenesulfonamide |  | Me | H | H |  |
| 43 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-(trifluoromethyl)benzenesulfonamide |  | Me | H | H |  |
| 44 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide |  | Me | H | H |  |
| 45 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-(trifluoromethoxy)benzenesulfonamide |  | Me | H | H |  |
| 46 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide |  | Me | H | H |  |

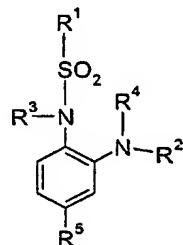
| | | | | | | |
|----|--|--|---|---|----|---|
| 47 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-methoxybenzenesulfonamide |  | Me | H | H |  |
| 48 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide |  | Me | H | H |  |
| 49 | N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide |  | Me | H | Et |  |
| 50 | N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-3,4-dimethoxybenzenesulfonamide |  | Me | H | Et |  |
| 51 | N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-7-quinolinesulfonamide |  | Me | H | Et |  |
| 52 | N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide |  | Me | H | Me |  |
| 53 | N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide |  | Me | H | Me |  |
| 54 | N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-5-(2-pyridinyl)-2-thiophenesulfonamide |  | Me | H | Me |  |
| 55 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide |  |  | H | H |  |
| 56 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-(dimethylamino)-1-naphthalenesulfonamide |  |  | H | H |  |

| 57 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-8-quinolinesulfonamide | | | H | H | |
|----|--|--|----|----|---|--|
| 58 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,4,6-trimethylbenzenesulfonamide | | | H | H | |
| 59 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide | | | H | H | |
| 60 | N-[5-(1,4-diazepan-1-yl)-2-({[(E)-2-phenylethyl]sulfonyl}amino)phenyl]benzenesulfonamide | | | H | H | |
| 61 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,5-dimethoxybenzenesulfonamide | | | H | H | |
| 62 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide | | | H | H | |
| 63 | 4-butoxy-N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide | | | H | H | |
| 63 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide | | | H | H | |
| 65 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-fluoro-2-methylbenzenesulfonamide | | | H | H | |
| 66 | N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-(methylsulfonyl)benzenesulfonamide | | | H | H | |
| 67 | N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide | | Me | Me | H | |

| | | | | | | |
|----|--|--|--|----|---|--|
| 68 | N-{5-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide | | | Me | H | |
|----|--|--|--|----|---|--|

TABLE II

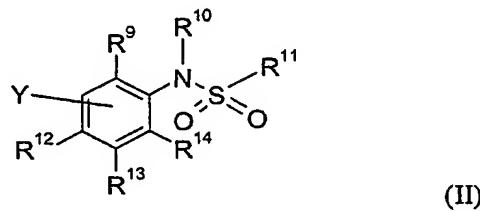
Compounds of the formula Ia



| | Name | R ¹ | R ³ | R ² | R ⁴ | R ⁵ |
|----|---|----------------|----------------|----------------|----------------|----------------|
| 69 | N-[2-amino-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide | | H | H | H | |
| 70 | N-[2-(ethylamino)-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide | | H | H | Et | |

Compounds of the Formula II

In a further aspect, the invention provides a compound having the general formula (II)



or a pharmaceutically acceptable salt thereof, wherein

R⁹, R¹² and R¹⁴ are H; or

10 two of R⁹, R¹² and R¹⁴ are H; and the remaining of R⁹, R¹² and R¹⁴ is

- (a) -NH₂,
- (b) -NHR⁶,
- (c) -NR⁶R⁷,
- (d) -N(CO)R⁶,
- 15 (e) -N(CS)R⁶, or
- (f) -NO₂;

R¹⁰ and R¹¹ is a group R³ or R¹ as defined for Formula I;

20 R¹³ is

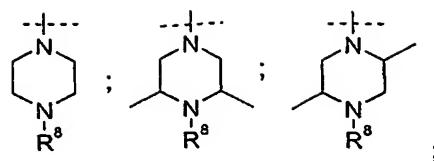
- (a) homopiperazine,
- (b) methylhomopiperazine or
- (c) a group R⁵ as defined for Formula I, wherein R⁸ is as defined for Formula I;

25 Y is as defined for Formula I.

Preferred compounds of the general formula (II) are those wherein:

R^{13} is

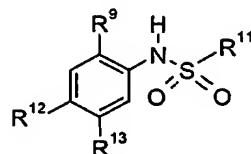
(a) homopiperazine,
(b) methylhomopiperazine, or
5 (c) a group R^5 selected from



R^8 is

(a) H, or
10 (b) C_{1-6} alkyl, in particular methyl;

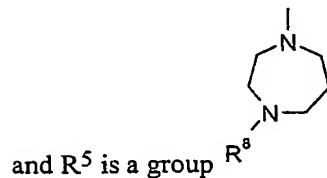
TABLE III

Compounds of the formula II wherein R¹⁰, R¹⁴ and Y are H

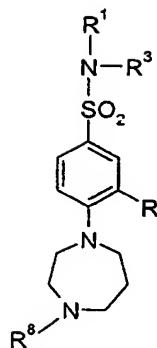
5

| | Name | R ⁹ | R ¹¹ | R ¹² | R ¹³ |
|----|---|------------------|-----------------|------------------|-----------------|
| 71 | 4-chloro-N-[5-(4-methyl-1,4-diazepan-1-yl)-2-nitrophenyl]benzenesulfonamide | -NO ₂ | | H | |
| 72 | N-[2-amino-5-(1,4-diazepan-1-yl)phenyl]benzenesulfonamide | -NH ₂ | | H | |
| 73 | N-[2-amino-5-(4-methyl-1,4-diazepan-1-yl)phenyl]benzenesulfonamide | -NH ₂ | | H | |
| 74 | N-[4-nitro-3-(1-piperazinyl)phenyl]benzenesulfonamide | H | | -NO ₂ | |
| 75 | N-[4-amino-3-(1-piperazinyl)phenyl]benzenesulfonamide | H | | -NH ₂ | |

TABLE IV

Compounds wherein Y and group -N-R² R⁴, is assigned as group R in the following structure

10

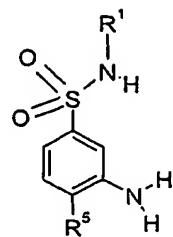


| | Name | R ¹ | R ³ | -R | R ⁸ |
|----|---|----------------|------------------|------------------|----------------|
| 76 | 3-amino-4-(1,4-diazepan-1-yl)-N-(4-methoxyphenyl)benzenesulfonamide | | H | -NH ₂ | H |
| 77 | 3-amino-4-(1,4-diazepan-1-yl)-N-(3-methoxyphenyl)benzenesulfonamide | | H | -NH ₂ | H |
| 78 | 3-amino-4-(1,4-diazepan-1-yl)-N-(2-methoxyphenyl)benzenesulfonamide | | H | -NH ₂ | H |
| 79 | 3-amino-4-(1,4-diazepan-1-yl)-N-(3-fluorophenyl)benzenesulfonamide | | H | -NH ₂ | H |
| 80 | 3-amino-4-(1,4-diazepan-1-yl)-N-methyl-N-phenylbenzenesulfonamide | | -CH ₃ | -NH ₂ | H |
| 81 | 3-amino-4-(1,4-diazepan-1-yl)-N-(4-isopropylphenyl)benzenesulfonamide | | H | -NH ₂ | H |
| 82 | 3-amino-4-(1,4-diazepan-1-yl)-N-(4-methylphenyl)benzenesulfonamide | | H | -NH ₂ | H |

| | Name | R ¹ | R ³ | -R | R ⁸ |
|----|--|----------------|----------------|------------------|------------------|
| 83 | 3-amino-4-(1,4-diazepan-1-yl)-N-(2,5-dimethylphenyl)benzenesulfonamide | | H | -NH ₂ | H |
| 84 | 3-amino-N-(3-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide | | H | -NH ₂ | H |
| 85 | 3-amino-N-(2-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide | | H | -NH ₂ | H |
| 86 | 3-amino-N-(2,4-dichlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide | | H | -NH ₂ | H |
| 87 | 3-amino-N-(2-methyl-5-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide | | H | -NH ₂ | H |
| 88 | 3-amino-N-(2-methyl-3-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide | | H | -NH ₂ | H |
| 89 | 3-amino-N-(4-trifluoro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide | | H | -NH ₂ | H |
| 90 | 3-amino-N-(4-fluorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide | | H | -NH ₂ | H |
| 91 | 3-amino-N-(2-fluorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide | | H | -NH ₂ | H |
| 92 | 3-amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide | | H | -NH ₂ | -CH ₃ |
| 93 | 4-(1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide | | H | -NO ₂ | H |
| 94 | 3-amino-4-(1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide | | H | -NH ₂ | H |

| | Name | R ¹ | R ³ | -R | R ⁸ |
|----|--|----------------|----------------|------------------|----------------|
| 95 | 2-(1,4-diazepan-1-yl)-5-(4-morpholinylsulfonyl)phenylamine | | | -NH ₂ | H |
| 96 | 4-(1,4-diazepan-1-yl)-N-phenyl-3-[(phenylsulfonyl)amino]benzenesulfonamide | | H | | H |
| 97 | 4-(1,4-diazepan-1-yl)-N-phenyl-3-[(methylsulfonyl)amino]benzenesulfonamide | | H | | H |

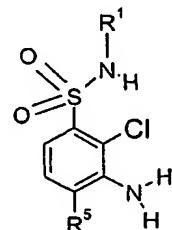
TABLE V

Compounds wherein Y, R³, R² and R⁴ are H

| | Name | R ¹ | R ⁵ |
|-----|---|----------------|----------------|
| 98 | 3-amino-N-(3-chlorophenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide | | |
| 99 | 3-amino-N-(2-methoxyphenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide | | |
| 100 | 3-amino-N-(2-methoxyphenyl)-4-(1-piperazinyl)benzenesulfonamide | | |
| 101 | 3-amino-N-(2-methoxyphenyl)-4-(3-methyl-1-piperazinyl)benzenesulfonamide | | |
| 102 | 3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-(2-methoxyphenyl)-benzenesulfonamide | | |
| 103 | 3-Amino-N-phenyl-4-piperazin-1-yl-benzenesulfonamide hydrochloride | | |
| 104 | 3-Amino-4-(3-methyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride | | |
| 105 | 3-Amino-4-(4-ethyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride | | |

| | Name | R ¹ | R ⁵ |
|-----|--|----------------|----------------|
| 106 | 3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-phenyl-benzenesulfonamide hydrochloride | | |
| 107 | 3-Amino-4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-N-phenyl-benzenesulfonamide hydrochloride | | |
| 108 | 3-Amino-4-(trans -2,5-dimethyl-piperazin-1-yl)-N-(2methoxy-phenyl)benzenesulfonamide hydrochloride | | |
| 109 | 2-(3-Amino-4-[1,4]diazepan-1-yl-benzenesulfonyl)-benzamide diacetic acid | | |
| 110 | 4-[4-(3-Fluoro-2-methoxy-phenylsulfamoyl)-2-amino-phenyl]-[1,4]diazepane ditrifluoroacetic acid | | |
| 111 | 2-[1,4]Diazepan-1-yl-5-(3,4-dihydro-1H-isoquinoline-2-sulfonyl)-aniline dihydrochloride | | |
| 112 | 4-[4-(3,4-Dihydro-2H-quinoline-1-sulfonyl)-2-amino-phenyl]-[1,4]diazepane ditrifluoroacetic acid | | |

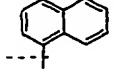
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| | Name | R ¹ | R ⁵ |
|--|------|----------------|----------------|
| | | | |

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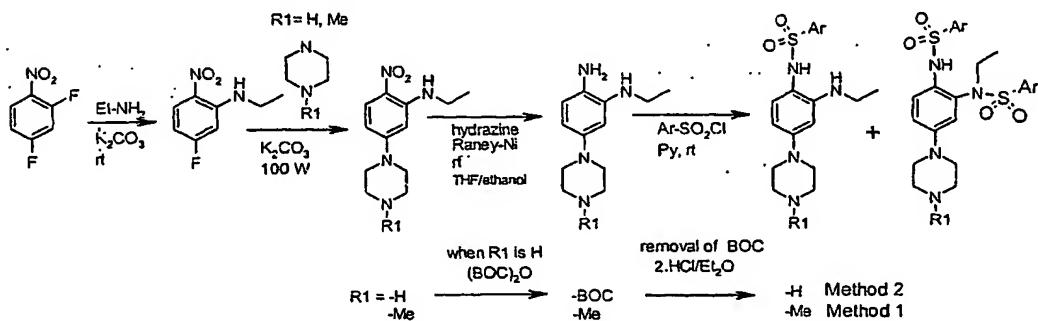
| | | | |
|-----|---|---|---|
| 113 | 3-Amino-2-chloro-N-naphthalen-1-yl-4-piperazin-1-yl-benzenesulfonamide, hydrochloride |  |  |
|-----|---|---|---|

The compounds in the tables are hydrochloride salts, reported if otherwise

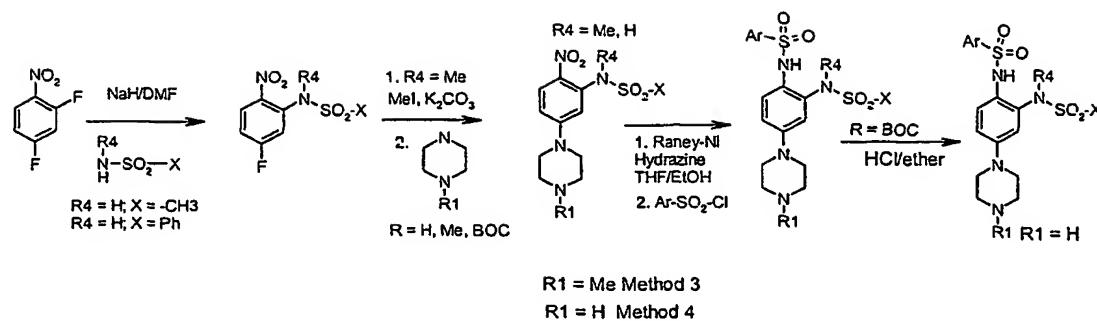
5 Processes for preparation

The compounds according to the invention having two sulfonyl groups were prepared according to the methods outlined in Schemes 1, 2 and 3.

10 Scheme 1

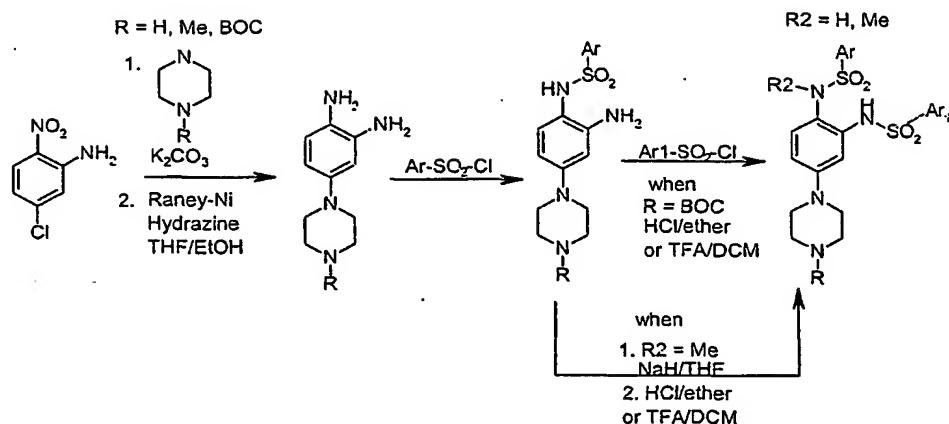


Scheme 2



5

Scheme 3



10

Depending on the process conditions the end products of the Formula I are obtained either in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

15

Acid addition salts of the new compounds may in a manner known *per se* be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

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In the preparation of acid addition salts, preferably such acids are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, 5 glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybensoic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, halogenbensenenesulfonic acid, toluenesulfonic acid, mandelic acid or naphthalenesulfonic acid.

10 Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. All diastereomeric forms possible (pure enantiomers, tautomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention. Such compounds can also occur as cis- or trans-, E- or Z- double bond isomer forms. All 15 isomeric forms are contemplated.

Pharmaceutical formulations

20 Pharmaceutical formulations are usually prepared by mixing the active substance, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutical excipients. The formulations can be further prepared by known methods such as granulation, compression, microencapsulation, spray coating, etc.

25 This invention relates to a method of treating obesity or type II diabetes. The method includes administering to a mammal subject (e.g., human) in need thereof an effective amount of one or more compounds of the formula (I) or the formula (II) above. Also within the scope of this invention is a method for modulating (e.g., inhibiting) 5-HT₆ receptor activity. The method includes administering to a mammal in need thereof an effective amount of a compound of the formula (I) or the formula (II) above.

30

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"An effective amount" refers to an amount of a compound which confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and preferably between 1 and 50% by weight in preparations for oral administration.

10 The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient and the route of administration. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance, preferably 50 to 150 mg per day.

15 The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

20

EXAMPLES

In the following examples, the structure of the prepared compounds were confirmed by standard spectroscopic methods and elemental analysis and/or high resolution MS. The 25 NMR data were obtained on a JEOL JNM-EX 270, a Bruker 400 DPX or a Bruker DRX 500 spectrometer. IR spectra were obtained on a Perkin Elmer SPECTRUM 1000 FT-IR spectrometer. High resolution MS were obtained on a Micromass LCT spectrometer. Elemental analysis was performed by Mikro Kemi AB Uppsala Sweden. Melting points, when given, were obtained on a Büchi or a Gallenkamp melting point apparatus and are 30 uncorrected.

Synthesis according to Scheme 1, Method 2 (R = Boc)**INTERMEDIATE 1****5 Synthesis of N-Ethyl-5-fluoro-2-nitroaniline.**

A suspension of 2,4-difluoro-1-nitrobenzene (0.50 g, 0.003 mmol), ethylamine hydrochloride (0.49 g, 0.006 mmol), K_2CO_3 (1.66 g, 0.012 mmol) in acetonitrile (30 mL) was stirred at room temperature for 16 hours and then filtered. The filtrate was concentrated and dissolved in small amount of $CHCl_3$. Purification by column chromatography on silica using pentane/diethyl ether 95:5 as eluent gave 0.45 g of a yellow solid. 1H NMR ($CDCl_3$) δ 8.23-8.18 (m, 1H), 8.08 (br s, 1H), 6.49-6.45 (m, 1H), 6.38-6.32 (m, 1H), 3.34-3.27 (m, 2H), 1.38 (tr, J = 7.22 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.55 (d, J_{CF} = 255.6 Hz), 147.4 (d, J_{CF} = 12.9 Hz), 129.91 (d, J_{CF} = 12.9 Hz), 128.71 (br s), 103.73 (d, J_{CF} = 24.8 Hz), 99.14 (d, J_{CF} = 27.6 Hz), 37.88, 14.05; MS (posESI) m/z = found 184.0653, calc 184.0648. Anal. ($C_{12}H_{18}N_4O_2$) C, H, N.

INTERMEDIATE 2**Synthesis of N-Ethyl-2-nitro-5-(1-piperazinyl)aniline.**

20 A suspension of N-ethyl-5-fluoro-2-nitroaniline (1.5 g, 8.12 mmol), piperazine (0.979 g, 11.37 mmol), K_2CO_3 (3.36 g, 24.3 mmol) in DMF (40 mL) was heated in a microwave oven for 1 min at 100 W. The reaction mixture was allowed to cool and then heated for another minute at 100W. This procedure was repeated 5 times. The suspension was filtered and then concentrated. The crude oil was purified via flash chromatography on silica using $CHCl_3/MeOH/NH_3$ 9:1:0.4% as eluent to give 1.53 g (75%) of a yellow solid. 1H NMR ($CDCl_3$) δ 8.30 (br s, 1H), 8.08-8.04 (m, 1H), 6.25-6.20 (m, 1H), 5.88-5.86 (m, 1H), 3.39-3.28 (m, 6H), 3.03-2.97 (m, 4H), 1.37 (tr, J =7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 156.27, 147.74, 128.96, 124.13, 104.28, 93.34, 48.22, 45.99, 37.73, 14.15; MS (posEI) m/z = 250 (M^+); MS (posESI) m/z = found 250.1429, calc 250.1430. Anal. ($C_{12}H_{18}N_4O_2$) C, H, O.

30

INTERMEDIATE 3

Synthesis of tert-Butyl 4-[3-(ethylamino)-4-nitrophenyl]-1-piperazinecarboxylate.

To a solution of N-ethyl-2-nitro-5-(1-piperazinyl)aniline (1.020 g, 4.075 mmol), and NaOH (0.39 g, 2.45 mmol) in THF:H₂O (64 mL, 1:1) was added a solution of di-tertbutyl-dicarbonate (2.67 g, 12.2 mmol) in 5 mL THF. The solution was stirred at room temperature for 16 hours. The mixture was neutralized with 1 N HCl. The volatiles were removed under vacuum to yield 1.4 g of crude material (98%). ¹H NMR (CDCl₃) δ 8.28 (br s, 1H), 8.13-8.09 (m, 1H), 6.27-6.22 (m, 1H), 6.05-6.02 (m, 1H), 3.67-3.61 (m, 4H), 3.45-3.38 (m, 4H), 3.35-3.27 (m, 2H), 1.50 (s, 9H); MS (posESI) m/z = found 350.1951, calc 350.1954.

10

INTERMEDIATE 4**Synthesis of tert-Butyl 4-[4-amino-3-(ethylamino)phenyl]-1-piperazinecarboxylate.**

To a solution of tert-butyl 4-[3-(ethylamino)-4-nitrophenyl]-1-piperazinecarboxylate (1.028 g, 2.93 mmol) in 40 mL EtOH:THF (4:1) solvent system was added Raney-Ni (1 mL of a EtOH suspension) followed by addition hydrazine hydrate (0.734 g, 14.67 mmol). The mixture was stirred vigorously for 3 hours and then filtered through a Celite pad pretreated with water. The filtrate was concentrated and then purified by column chromatography on silica using CHCl₃/MeOH/NH₃ 9:1:0.4% as eluent to give 0.877 g (93%) of a red oil. The oil was used immediately in the next reaction. HPLC purity >90 %; MS (posEI) m/z = 320 (M⁺);

Method 1, Scheme 1: General for sulfonylation (R1 = Me)**INTERMEDIATE 5**

25

Synthesis of N-ethyl-5-(4-methyl-1-piperazinyl)-2-nitroaniline (Method 1, Scheme 1)

N-ethyl-5-(4-methyl-1-piperazinyl)-2-nitroaniline was prepared from 2,4-difluoro-1-nitrobenzene and methylpiperazine using the same method described for N-ethyl-2-nitro-5-(1-piperazinyl)aniline and was obtained as yellow solid (99 %). ¹H NMR (CDCl₃) δ 8.30 (br s, 1H), 8.08-8.04 (m, 1H), 6.25-6.20 (m, 1H), 5.89-5.86 (m, 1H), 3.45-3.39 (m, 4H), 3.35-3.25 (m, 2H), 2.56-2.50 (m, 4H), 2.35 (s, 3H), 1.37 (tr, J=7.2 Hz, 3)); ¹³C NMR δ (CDCl₃)

155.92, 147.72, 128.99, 124.19, 104.30, 94.37, 54.78, 47.05, 46.25, 37.73, 14.43; MS (posESI) m/z = found 264.1575, calc 264.1586. Anal. (C₁₃H₂₀N₄O₂·0.5 H₂O) C, H, O.

INTERMEDIATE 6

5

Synthesis of N-2-Ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (Method 1, Scheme 1)

N-Ethyl-5-(4-methyl-1-piperazinyl)-2-nitroaniline was reduced with Raney-Ni as described previously for the synthesis of tert-butyl 4-[4-amino-3-(ethylamino)phenyl]-1-piperazinecarboxylate to give N-2-ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (yield >90%) as a red oil. The product is very sensitive to oxidation and was therefore used immediately in the next reaction step. HPLC purity >90 %; MS (posEI) m/z = 234 (M⁺);

EXAMPLE 1

15

N-[2-{Ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride (Method 1, Scheme 1)

To a solution of amine N-2-ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (0.200 g, 0.853 mmol) and pyridine (0.48 mL, 5.97 mmol) in CH₂Cl₂ (8 mL) was added a solution of 3-fluorobenzenesulfonyl chloride (249 mg, 1.28 mmol) in CH₂Cl₂ (2 mL). The mixture was stirred at room temperature for 16 hours. CH₂Cl₂ (10 mL) was added and the mixture was washed with saturated aqueous NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and concentrated. Purification by column chromatography (Al₂O₃, EtOAc/MeOH 9.5:0.5) gave two products. The first fraction contained 110 mg of N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride. The second fraction contained 100 mg of N-[2-(ethylamino)-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride. Both products were converted to the HCl-salts.

N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride: ¹H NMR (DMSO-*d*6) δ 11.14 (br s, 1H), 9.27 (s, 1H), 7.75-7.35 (m, 8H), 7.18-7.15 8m, 1H), 6.95-6.90 (m, 1H), 6.07-6.04 (m, 1H), 3.47-3.30

(m, 4H), 3.05-2.85 (m, 4H), 2.73 8d, J=4.7 Hz), 0.72 (tr, J=7.2Hz); ^{13}C NMR (CD₃OD) δ 162.65 (d, J_{CF}=5.5 Hz), 160.68 (d, J_{CF}=4.6 Hz), 146.61, 142.52 (d, J_{CF}=7.4 Hz), 139.04 (d, J_{CF}=6.4 Hz), 131.58 (131.63, 131.28, 128.67, 124.25, 123.14, 122.89, 120.56 (d, J_{CF}=21 Hz), 120.05 (d, J_{CF}=21 Hz), 116.52, 115.64, 114.80 (d, J_{CF}=25Hz), 113.97 (d, J_{CF}=25 Hz), 51.88, 5 45.82, 44.84, 41.79, 12.31; Ms (posES-FIA) *m/z* = 551 (M+H)

EXAMPLE 2

N-[2-[ethyl(phenylsulfonyl)amino]-4-(4-methyl-1-piperazinyl)phenyl]- benzenesulfonamide hydrochloride (Scheme 1, Method 1)

10 N-[2-[ethyl(phenylsulfonyl)amino]-4-(4-methyl-1-piperazinyl)phenyl]-
benzenesulfonamide hydrochloride was prepared as described in Scheme 1. Sulfonylation
from N-2-ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine and phenylsulfonyl chloride
was performed as described in Method 1. Purification by chromatography (SiO₂,
chloroform:methanol:NH₃ 9:1:0.4%) followed by trituration with MeOH gave 68 mg (15%
15 yield) of the free base which was converted to its HCl-salt. MS (posES-FIA) *m/z* = found:
514.1700, calc: 514.1708; Anal. (C₂₅H₃₀N₄O₄S₂.2HCl) C, H, N.

EXAMPLE 3

20 3-Fluoro-N-[2-{{(3-fluorophenyl)sulfonyl}amino}-4-(4-methyl-1- piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 3)

Synthesis of 2-Amino-5-(4-methyl-1-piperazinyl)aniline. A mixture of 2-nitro-3-
chloroaniline (4.47g, 25.9 mmol), methylpiperazine (3.1 g, 31 mmol) and K₂CO₃ (5.41g, 39
mmol) in acetonitrile was stirred at 70 °C for 48 h. The mixture was filtered and purified by
25 column chromatography (SiO₂, CH₂Cl₂/MeOH/Heptane/NH₃ 4:1:5 x 0.2 %) to give 1.6 g of
product (unreacted starting material was isolated): ^1H -NMR δ 7.66-7.45 (m, 5H), 6.78 (d,
1H), 6.62 (d, 1H), 6.50 (dd, 1H), 3.39-3.35 (m, 4H), 3.02-2.99 (m, 4H); MS (posES-FIA) *m/z*
333.0 (M⁺ + H). The product (1.06 g, 4.49 mmol) was dissolved in EtOH:THF (4:1). Raney-
Ni and hydrazine (1.12 mL, 22 mmol) were added. The reaction was stirred at room
30 temperature for 3 h until the yellow color disappeared. Filtration through wet Celite pad,
followed by removal of the solvent afforded 0.802 g of 2-amino-5-(4-methyl-1-

5 piperazinyl)aniline which was used without further purification in the next step. 3-
Fluorobenzenesulfonyl chloride (0.133 g, 0.68 mmol) was added to a solution of 2-amino-5-
(4-methyl-1-piperazinyl)aniline (0.141 g, 0.68 mmol) and pyridine (514 mL, 6.39 mmol) in
CH₂Cl₂. After 1 h the mixture was washed with aq NaHCO₃ (10 %), dried (MgSO₄) and the
solvent was removed. Purification by chromatography (SiO₂, CH₂Cl₂/methanol/heptane,
4:1:5) gave 3-fluoro-N-[2-amino-4-(4-methyl-1-piperazinyl)-phenyl]benzenesulfonamide
(0.140 g, 57 %). MS (posES-FIA) *m/z* = found: 365.2, calcd: 364.14; Anal.
(C₁₇H₂₂ClFN₄O₂S·3H₂O) C, H, N, S. The reaction produced a small amount of bis-
sulfonylated compound 3-fluoro-N-[2-{[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-
10 piperazinyl)-phenyl]benzenesulfonamide (0.010 g, 3 %). The products were transformed into
their HCl-salt before analysis; MS (posES-FIA) *m/z* = found. 523.5, calcd: 522.12. Anal.
(C₂₃H₂₅ClF₂N₄O₄S₂) C, H, N, S.

EXAMPLE 4

15

N-{4-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-8- quinolinesulfonamide hydrochloride (Scheme 3)

8-Quinolinesulfonyl chloride (0.185 g, 0.81 mmol) was added to a solution of 2-
amino-5-(4-methyl-1-piperazinyl)aniline (0.168 g, 0.81 mmol) and pyridine (514 mL, 6.39
20 mmol) in CH₂Cl₂. After 1 h at room temperature the mixture was washed with aq NaHCO₃
(10 %), dried (MgSO₄) and the solvent was removed. Purification by chromatography (SiO₂,
CH₂Cl₂/MeOH/heptane, 4:1:5) gave N-2-amino-4-(4-methyl-1-piperazinyl)-]-phenyl-8-
quinolinesulfonamide (0.110 g, 35 %). MS (posES-FIA) *m/z* = found: 384.2, calcd 383.48;
25 %); Anal. (C₁₉H₂₂ClN₅O₂S·3H₂O) C, H, N, S and a small amount of the bis-sulfonylated N-
{4-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-8-
quinolinesulfonamide (0.070 g, 15 %). The product was converted to HCl salt before
analysis; MS (posES-FIA) *m/z* = found: 589.6, calcd: 588.16; Anal. (C₂₉H₂₉ClN₆O₄S₂·2H₂O)
C, H, N.

30 **Synthesis according to Scheme 2****Scheme 2, Method 3: General R1 = Me**

INTERMEDIATE 7

Synthesis of N-(5-fluoro-2-nitrophenyl)benzenesulfonamide (Scheme 2, Method 3)

5 Benzenesulfonamide (3.14 g, 20 mmol) was dissolved in DMF (100 mL) and NaH (60% in oil, 40 mmol, 1.60 g) was added. The reaction was stirred until the gas evolution ceased. 2,4-Difluoronitrobenzene (18 mmol, 2.9 g, 2 mL) was added and the reaction mixture was stirred over night at 35°C. The reaction mixture was poured into HCl (1M aq, 100 mL) and extracted with toluene (25 mL x 5). The organic phase was dried (MgSO_4) and 10 concentrated and re-crystallized from EtOH to give a first crop of 3.75 g of a yellow solid. A second crop of 0.20 g was collected from the EtOH remains. Yield 3.95 g, 13.3 mmol (74%). MS (posES-FIA) m/z = found: 296; Calc: 296,0.

INTERMEDIATE 8

15 **Synthesis of N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]benzenesulfonamide (Scheme 2, Method 3)**

16 N-(5-fluoro-2-nitrophenyl)benzenesulfonamide (2 x 0.50 g, 1.688 mmol) was treated with N-methyl-piperazine (2 x 4.65 g, 45.6 mmol) and put in two pyrex tubes and sealed. 20 Each tube was put in a LabWell MW-10 microwave oven for 2 min at 50W. The reaction mixtures were combined and poured into 0.5 M NaOH (aq) and extracted with CH_2Cl_2 , dried (MgSO_4) and concentrated to give 0.99 g, (2.63 mmol) in 78% yield as a yellow solid. Anal ($\text{C}_{17} \text{H}_{20} \text{N}_4 \text{O}_4 \text{S}$) C, H, N, S; MS (posES-FIA) m/z = found: 377.4; Calcd: 376.12.

25 EXAMPLE 5

N-[2-Chloro-4-({4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]-anilino}sulfonyl)phenyl]acetamide hydrochloride (Scheme 2, Method 3)

26 N-[5-(4-Methyl-1-piperazinyl)-2-nitrophenyl]benzenesulfonamide (0.600 g, 1.59 mmol) was dissolved in THF (20 mL) followed by the addition of Raney-Ni (0.322 g, in ethanol) and hydrazine hydrate (0.100 g, 2.0 mmol). The reaction mixture was stirred for 1h,

filtered through Celite and concentrated. The residue was dissolved in pyridine (12 mL) and divided in 12 equal parts. To one part was added 3-chloro-4-N-acetamido-benzenesulfonylchloride (52 mg, 0.20 mmol). The reaction mixture was stirred over night, poured into petroleum ether to form a precipitate that was collected by centrifugation. The precipitate purified by column chromatography (SiO₂, CH₂Cl₂/MeOH 95:5 to 9:1). The pure product was dissolved in MeOH and treated with HCl/diethyl ether to give 9.6 mg, (12% yield). MS (posES-FIA) *m/z* found: 578.4; Calcd: 577.12.

EXAMPLE 6

10

3,4-Dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)-amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)

N-[5-(4-Methyl-1-piperazinyl)-2-nitrophenyl]benzenesulfonamide (0.600 g, 1.59 mmol) was dissolved in THF (20 mL) followed by the addition of Raney-Ni (0.322 g, in ethanol) and hydrazine hydrate (0.100 g, 2.0 mmol). The reaction mixture was stirred for 1h, filtered through Celite and concentrated. The residue was dissolved in pyridine (12 mL) and divided in 12 equal parts. To one part was added 3,4-dimethoxy-benzenesulfonylchloride (47 mg, 0.20 mmol). The reaction mixture was stirred overnight, poured into petroleum ether to form a precipitate that was collected by centrifugation. The precipitate was purified by column chromatography (SiO₂, CH₂Cl₂/MeOH 95:5 to 9:1). The pure product was dissolved in MeOH and treated with HCl/diethyl ether to give 34.5 mg, (45% yield). MS (posES-FIA) *m/z* found: 547.4; Calcd: 546.16.

EXAMPLE 7

25

3-Methoxy-4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)-amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)

N-[5-(4-Methyl-1-piperazinyl)-2-nitrophenyl]benzenesulfonamide (0.600 g, 1.59 mmol) was dissolved in THF (20 mL) followed by the addition of Raney-Ni (0.322 g, in ethanol) and hydrazine hydrate (0.100 g, 2.0 mmol). The reaction mixture was stirred for 1h, filtered through Celite and concentrated. The residue was dissolved in pyridine (12 mL) and

divided in 12 equal parts. To one part was added 2-methoxy-4-methylbenzenesulfonylchloride (44 mg, 0.20 mmol). The reaction mixture was stirred overnight, poured into petroleum ether to form a precipitate that was collected by centrifugation. The precipitate was purified by column chromatography (SiO₂, CH₂Cl₂/MeOH 95:5 to 5:1). The pure product was dissolved in MeOH and treated with HCl/diethyl ether to give 21 mg, (28% yield). MS (posES-FIA) *m/z* = found: 530.1635; Calcd: 530.1658.

INTERMEDIATE 9

10 **Synthesis of N-(5-fluoro-2-nitrophenyl)methanesulfonamide (Scheme 2, Method 3)**

Methylsulfonamide (2.421 g, 25.4 mmol) was dissolved in DMF (100 mL) and NaH (60% in oil, 1.00 g, 25 mmol) was added. The reaction stirred for 1 h and added to a stirred solution of 2,4-difluoronitrobenzene (4.372 g, 27.5 mmol) in DMF (20 mL). The reaction mixture was stirred for 2h, poured into a mixture (1:1) of brine and 1M HCl, and extracted with toluene. The organic phase was dried (MgSO₄), and concentrated to give a solid that was crystallized from toluene / petroleum ether: The flask tipped over and some material was lost, to give 1.32 g, 5.64 mmol in 22% yield. MS (posES-FIA) *m/z* = found: 234; Calcd: 234.01; Anal (C₇ H₇ F N₂ O₄ S), C, H, N, S.

20 **INTERMEDIATE 10**

Synthesis of N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]-methanesulfonamide (Scheme 2, Method 3).

N-(5-fluoro-2-nitrophenyl)methanesulfonamide (1.33 g, 5.68 mmol) was dissolved in 25 DMF (10 mL) and N-methylpiperazine (2.00 g, 20 mmol) was added. The reaction mixture was stirred at 20°C for 1h, and then heated with a heat gun for 5 min to reach boiling of DMF (150°C), then left stirring for another hour. The reaction mixture was then poured into brine and extracted with toluene (10 mL x 2), EtOAc (20 mL x 2) and CH₂Cl₂ (20 mL x 2), NaHCO₃ was then added to the water phase and then the water phase was extracted with 30 CH₂Cl₂ (20 mL x 2). The organic phases were combined and dried (MgSO₄) and concentrated to give a semi solid. EtOH was added and left over night and then filtered off to

give 1.503 g (4.78 mmol) in 84 % yield. MS (posES-FIA) *m/z* = found: 315; Calc M=314.10; Anal (C₁₂ H₁₈ N₄ O₄ S), C, H, N, S.

EXAMPLE 8

5

4-Methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]-phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)

N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]-methanesulfonamide (0.45 g, 1.43 mmol) was dissolved in THF (10 mL) followed by the addition of Raney-Ni (0.15 g in ethanol) and hydrazine hydrate (78 mg, 1.56 mmol). The reaction was stirred for 1h. Another aliquot of hydrazine hydrate (20 μ L) was added and the reaction stirred for another hour, filtered through Celite and concentrated to give 0.42 g that was used to the next step without further purification. The material was dissolved in DMF (10 mL) and divided into 3 equal parts. To one part was added *p*-toluene sulfonyl chloride (0.095 g, 0.5 mmol) and the reaction was stirred for 1 h and poured into a mixture of petroleum ether/acetone (30 mL/10 mL) to give a precipitate. Additional product was found in the solution and added to the precipitate. The product was isolated by chromatography (SiO₂, CH₂Cl₂/MeOH 9:1) to give 0.063 g, (28% yield). MS (posES-FIA) *m/z* = found: 38.1393; Calcd: 438.1395.

20

EXAMPLE 9

3,4-Dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]-phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)

N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]-methanesulfonamide (0.45 g, 1.43 mmol) was dissolved in THF (10 mL) and Raney-Ni (0.15 g in ethanol) was added followed by hydrazine hydrate (78 mg, 1.56 mmol) and the reaction was stirred for 1h. Additional hydrazine hydrate (20 μ L) was added and the reaction stirred for another hour, filtered through Celite and concentrated to give 0.42 g of product that was used without further purification. The material was dissolved in DMF (10 mL) and divided into 3 equal parts. To one part was added 3,4 dimethoxybenzenesulfonylchloride (0.118 g, 0.5 mmol) and the reaction was stirred for 1 h, poured into a mixture of petroleum ether/acetone (30 mL/10 mL)

to form a precipitate. Additional product was found in the solution and was added to the precipitate. The product was isolated by chromatography (SiO₂, CH₂Cl₂/MeOH 9:1) to give 0.064 g, (26% yield). MS (posES-FIA) *m/z* = found: 484.1436; Calcd: 484.1450.

EXAMPLE 10

5

3-Cyano-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]-phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 3)

N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]-methanesulfonamide (0.45 g, 1.43 mmol) was dissolved in THF (10 mL) and Rayney-Ni (0.15 g in ethanol) was added followed 10 by hydrazine hydrate (78 mg, 1.56 mmol) and the reaction was stirred for 1h. Additional hydrazine hydrate (20 μ L) was added and the reaction stirred for another hour, filtered through Celite and concentrated to give 0.42 g of product that was used without further purifications. The material was dissolved in DMF (10 mL) and divided into 3 equal parts. To 15 one part was added 3-cyanobenzenesulfonylchloride (0.101 g, 0.5 mmol) and the reaction was stirred for 1 h. poured into a mixture of petroleum ether/acetone (30 mL/10 mL) to form a precipitate. Additional product was found in the solution and was combined to the precipitate. The product was isolated by chromatography (SiO₂, CH₂Cl₂/MeOH 9:1) to give 0.0301g, (13% yield). MS (posES-FIA) *m/z* = found: 449.1177; Calcd: 449.1191.

20 **Scheme 2, Method 4: General R1 = H**

N-(2-amino-5-(4-boc-1-piperazinyl)-phenyl)-benzenesulfonamide

A mixture of N-(2-nitro-3-fluorophenyl)-benzenesulfonamide (4.68 g, 15.7 mmol), Boc-piperazine (3.5 g, 18.9 mmol) and K₂CO₃ (3.8 g, 27.8 mmol) in DMF was stirred at 70°C for 24h. The mixture was filtered and purified by column chromatography (SiO₂, 25 CH₂Cl₂/MeOH/heptane/NH₃ 4:1:5:0.2 %) to give 2.0 g of desired product. ¹H-NMR δ 7.98 (d, 1H), 7.89-7.84 (m, 2H), 7.63-7.50 (m, 3H), 7.00 (d, 1H), 6.68 (dd, 1H), 3.59-3.45 (m, 8H), 1.49 (s, 9H); MS (posES-FIA) *m/z* = found: 485.0 (M⁺ + Na⁺). The product (1.85 g, 4.00 mmol) was dissolved in EtOH:THF (4:1) followed by addition of Raney-Ni and 30 hydrazine (1.0 mL, 20 mmol). The reaction was stirred at room temperature for 3 h until the yellow color disappeared. Filtration through wet Celite, followed by removal of the solvent

afforded 1.26 g of N-(2-amino-5-(4-tert-butoxycarbonyl-1-piperazinyl)-phenyl)-benzenesulfonamide which was used without further purification.

To a solution of N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide (79 mg, 0.184 mmol) and pyridine (131 μ L, 1.6 mmol) in CH₂Cl₂ (7 mL) and different sulfonylchlorides (0.239 mmol) was added. After 2 h at room temperature the solvent was removed. Purification by chromatography (SiO₂, CH₂Cl₂/MeOH/heptane, 4:1:15) followed by Boc-deprotection which was achieved by dissolving the residue in small amount of MeOH and adding HCl/ether. The mixture was left at room temperature for 0.5 h after which the solvent was removed. Re-crystallization (MeOH/ether) afforded the final products respectively.

EXAMPLE 11

N-{4-(1-Piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride (Scheme 2, Method 4)

N-{4-(1-Piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 1-naphthalenesulfonylchloride (54 mg, 0.239 mmol) according to general method 3 to give 40 mg of a purple solid. MS (posES-FIA) m/z = Found: 523.2; Calcd 523.14; ¹H NMR δ 8.83-8.59 (m, 1H), 8.10 (d, 1H), 8.02-7.97 (m, 1H), 7.90 (d, 1H), 7.74-7.38 (m, 8H), 6.69-6.65 (m, 1H), 6.39-6.34 (m, 2H), 3.35-3.14 (m, 8H).

EXAMPLE 12

25

5-(Dimethylamino)-N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride (Scheme 2, Method 4)

5-(Dimethylamino)-N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and dansylchloride (64 mg, 0.239 mmol) according to general method 3 to give 60 mg of a purple solid. MS (posES-FIA) m/z =

Found: 566.3; Calcd: 566.18; ^1H NMR δ 8.84 (d, 1H), 8.60 (d, 1H), 8.08 (d, 2H), 7.84-7.47 (m, 7H), 6.70 (d, 1H), 6.56-6.53 (m, 1H), 6.41-6.37 (m, 1H), 3.46 (s, 6H), 3.25-3.12 (m, 8H).

EXAMPLE 13

5

N-[2-[(Phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide hydrochloride (Scheme 2, Method 4)

$\text{N-[2-[(Phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide}$ was synthesized from $\text{N-}\{\text{2-amino-5-(4-}t\text{-butyloxycarbonyl-piperazinyl)-phenyl}\}\text{benzenesulfonamide}$ and $\text{8-quinolinesulfonylchloride}$ (54 mg, 0.239 mmol) according to general method 3 to give 50 mg of a purple solid. MS (posES-FIA) m/z = Found: 524.2; Calcd: 524.13; ^1H NMR δ 9.34 (dd, 1H), 8.79 (dd, 1H), 8.37 (dd, 1H), 8.25 (dd, 1H), 7.92 (dd, 1H), 7.73 (t, 1H), 7.57-7.40 (m, 5H), 7.17 (d, 1H), 6.71 (dd, 1H), 6.14 (d, 1H), 3.23-3.08 (m, 8H).

15

EXAMPLE 14

2,4,6-Trimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)

2,4,6-Trimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from $\text{N-}\{\text{2-amino-5-(4-}t\text{-butyloxycarbonyl-piperazinyl)-phenyl}\}\text{benzenesulfonamide}$ and $\text{2-mesitylenesulfonylchloride}$ (52 mg, 0.239 mmol) according to general method 3 to give 50 mg of a purple solid. MS (posES-FIA) m/z = Found: 515.3; Calcd 515.17; $^1\text{H-NMR}$ δ 7.74 (d, 2H); 7.63-7.46 (m, 3H), 6.92 (s, 2H), 6.74-6.55 (m, 3H), 3.27-3.20 (m, 8H), 2.35 (s, 6H), 2.25 (s, 3H).

EXAMPLE 15

4-Methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide hydrochloride (Scheme 2, Method 4)

4-Methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and p-toluenesulfonylchloride (46 mg, 0.239 mmol) according to general method 3 to give 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 487.2; Calcd: 487.14; $^1\text{H-NMR}$ δ 7.73-7.45 (m, 7H), 7.26 (d, 2H), 6.74 (s, 1H), 6.62-6.60 (m, 2H), 3.69 (app t, 2H), 3.39 (app t, 2H), 3.29-3.74 (m, 4H), 2.38 (s, 3H).

EXAMPLE 16

10

N-[2-({[(E)-2-Phenylethenyl]sulfonyl}amino)-5-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)

15

N-[2-({[(E)-2-Phenylethenyl]sulfonyl}amino)-5-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and β -styrenesulfonylchloride (48 mg, 0.239 mmol) according to general method 3 to give before Boc-deprotection 160 mg of a purple solid. MS (posES-FIA) m/z = Found: 499.2; Calcd 499.14; $^1\text{H-NMR}$ δ 8.26 (d, 1H), 8.04 (d, 1H), 7.75-7.38 (m, 8H), 7.22 (d, 1H, J = 15.4 Hz), 7.16 (d, 1H), 6.97 (d, 1H, J = 15.4 Hz), 6.78 (dd, 1H), 6.68 (d, 1H), 3.68 (app t, 2H), 3.39 (app t, 2H), 3.28-3.21 (m, 4H).

20

EXAMPLE 17

2,5-Dimethoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)

25

2,5-Dimethoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 2,5-dimethoxybenzenesulfonylchloride (57 mg, 0.239 mmol) according to general method 3 to give 60 mg of a purple solid. MS (posES-FIA) m/z = Found: 533.1; Calcd: 533.14; $^1\text{H-NMR}$ δ 7.68-7.48 (m, 5H), 7.16-7.05 (m, 4H), 6.69 (dd, 1H), 6.42 (d, 1H), 4.03 (s, 3H), 3.69 (s, 3H), 3.26-3.10 (m, 8H).

EXAMPLE 18

2-Methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide hydrochloride (Scheme 2, Method 4)

5 2-Methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and o-toluenesulfonylchloride (46 mg, 0.239 mmol) according to general method 3 to give before Boc-deprotection 160 mg of a purple solid. MS (posES-FIA) m/z = Found: 487.1; Calcd 487.14; ¹H-NMR δ 7.74-7.16
10 (m, 8H), 6.78-6.52 (m, 4H), 3.27-3.16 (m, 8H), 2.58 (s, 3H).

EXAMPLE 19

15 **2,4-Difluoro-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide hydrochloride (Scheme 2, Method 4)**
2,4-Difluoro-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 2,4-difluorobenzenesulfonylchloride (94 mg, 0.455 mmol) according to general method 3 to give before Boc-deprotection 160 mg of a
20 purple solid. MS (posES-FIA) m/z = Found: 509.1; Calcd 509.11; ¹H-NMR δ 77.71-7.46 (m, 6H), 7.25-7.17 (m, 1H), 7.03-6.96 (m, 2H), 6.72 (dd, 1H), 6.44 (d, 1H), 3.20-3.16 (m, 8H).

EXAMPLE 20

25 **4-Butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide hydrochloride (Scheme 2, Method 4)**
4-Butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)- phenyl}benzenesulfonamide and 4-*n*-butoxybenzenesulfonylchloride (59 mg, 0.239 mmol) according to general method 3 to give

70 mg of a purple solid. MS (posES-FIA) m/z = Found: 545.2; Calcd 545.18; $^1\text{H-NMR}$ δ 7.73-7.45 (m, 7H), 6.95-6.91 (m, 2H), 6.72-6.70 (m, 1H), 4.00 (t, 2H), 3.29-3.24 (m, 8H), 1.79-1.70 (m, 2H), 1.55-1.43 (m, 2H), 0.97 (t, 3H).

5 EXAMPLE 21

3,5-Dimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-4-isoxazolesulfonamide hydrochloride (Scheme 2, Method 4)

3,5-Dimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-4-isoxazolesulfonamide was synthesized from N-{2-amino-5-(4-t-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 3,5-dimethylisoxazolesulfonylchloride (47 mg, 0.239 mmol) according to general method 3 to give 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 492.1; Calcd 492.13; $^1\text{H-NMR}$ δ 7.72-7.47 (m, 5H), 6.98 (d, 1H), 6.80 (dd, 1H), 6.50 (d, 1H), 3.28-3.22 (m, 8H), 2.22 (s, 3H), 2.11 (s, 3H).

15

EXAMPLE 22

5-Fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide (Scheme 2, Method 4)

5-Fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)-phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-t-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 5-fluoro-2-methylbenzenesulfonylchloride (50 mg, 0.239 mmol) according to general method 3 to give 60 mg of a purple solid. MS (posES-FIA) m/z = Found: 505.2; Calcd 505.13; $^1\text{H-NMR}$ δ 7.73-7.17 (m, 8H), 6.83 (d, 1H), 6.68 (dd, 1H), 6.50 (dd, 1H), 3.27-3.17 (m, 8H), 2.55 (s, 3H).

EXAMPLE 23

4-(Methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-benzenesulfonamide hydrochloride (Scheme 2, Method 4)

4-(Methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)-phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 4-methylsulfonylbenzenesulfonylchloride (61 mg, 0.455 mmol) according to general method 3 to give 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 551.2; Calcd: 551.10.

5 EXAMPLE 24

2-(Methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)

10 2-(Methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 2-methylsulfonylbenzenesulfonylchloride (61 mg, 0.239 mmol) according to general method 3 to give 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 551.2; Calcd: 551.10; ¹H-NMR δ 8.36-7.46 (m, 9H), 6.95 (d, 1H), 6.68 (dd, 1H), 6.46 (d, 1H), 3.47 (s, 3H), 3.28-3.17 (m, 8H).

15 EXAMPLE 25

20 **2-Methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)**

25 2-Methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 2-methoxy-4-methylbenzenesulfonylchloride (53 mg, 0.239 mmol) according to general method 3 to give 80 mg of a purple solid. MS (posES-FIA) m/z = Found: 517.2; Calcd 517.15; ¹H NMR δ 7.67-7.37 (m, 6H), 7.10-7.04 (m, 2H), 6.97-6.74 (m, 2H), 6.30 (d, 1H), 4.06 (s, 3H), 3.26-3.09 (m, 8H), 2.37 (s, 3H).

EXAMPLE 26

4-Methoxy-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 2, Method 4)

5 4-Methoxy-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-piperazinyl)-phenyl}benzenesulfonamide and 2-methyl-4-trifluoromethoxybenzenesulfonylchloride (53 mg, 0.455 mmol) according to general method 3 to give before Boc-deprotection 70 mg of a purple solid. MS (posES-FIA) m/z = Found: 10 571.2; Calcd 571.12; ^1H NMR δ 7.73-7.09 (m, 8H), 6.86 (d, 1H), 6.69 (dd, 1H), 6.48 (d, 1H), 3.29-3.17 (m, 8H), 2.62 (s, 3H).

EXAMPLE 27

15 **N-{4-(homopiperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 1, Method 2)**

15 Benzenesulfonyl chloride (0.088 g, 0.50 mmol) was added to a solution of 2-amino-5-(4-*t*-butyloxycarbonyl-homopiperazin-1-yl)aniline (0.153 g, 0.50 mmol) and pyridine (514 mL, 6.39 mmol) in DCM. After 1 h at r.t. the mixture was washed with NaHCO₃ (10 %) 20 dried (MgSO₄) and the solvent was removed. Purification by column chromatography (CH₂Cl₂/MeOH/heptane, 4:1:15) gave a mixture of N-{2-amino-4-[4-*t*-butyloxycarbonyl-homopiperazin-1-yl]-phenyl}benzenesulfonamide and of the bis-sulphonylated N-{4-[4-*t*-butyloxycarbonyl] homopiperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide (0.150 g, 86 %). Boc-deprotection was achieved by dissolving the mixture in MeOH and 25 adding HCl/ether. The mixture was let at r.t. for 0.5 h. Purification by preparative HPLC gave N-{4-(homopiperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride; Anal. (C₂₃H₂₇ClN₄O₄S₂) C, H, N, S ; M+ 487.4 Calcd 486.14. And N-{4-(homopiperazinyl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride; Anal. (C₁₇H₂₃ClN₄O₂S) C, H, N, S ; M+ 347.5 Calcd 346.15.

30

EXAMPLE 28

/O

N-(4-(1,4-diazepan-1-yl)-2-{{(3-fluorophenyl)sulfonyl]amino}phenyl)-3-fluorobenzenesulfonamide hydrochloride (Scheme 1, Method 2)

The compound was prepared from 2-amino-5-(4-*t*-butyloxycarbonyl-1-homopiperazinyl)aniline and 3-fluorobenzenesulfonyl chloride. Purification by column chromatography (CH₂Cl₂/MeOH/heptane, 4:1:15) gave a mixture of N-{2-amino-4-[4-*t*-butyloxycarbonyl-homopiperazin-1-yl]phenyl}3-fluorobenzenesulfonamide and N-{4-[4-*t*-butyloxycarbonyl] homopiperazinyl)-2-[(3-fluorophenylsulfonyl)amino]phenyl}-3-fluorobenzenesulfonamide (0.180 g, 73 %). Boc-deprotection was achieved by dissolving the mixture in small amount of MeOH and adding HCl/ether. The mixture was let at r.t. for 0.5 h. Purification by preparative HPLC gave N-(4-(1,4-diazepan-1-yl)-2-{{(3-fluorophenyl)sulfonyl]amino}phenyl)-3-fluorobenzenesulfonamide hydrochloride Anal. (C₂₃H₂₇ClN₄O₄S₂) C, H, N, S.; M⁺ 524.4 Calcd 522.12.

15 **EXAMPLE 29**

N-{4-(1,4-diazepan-1-yl)-2-[ethyl(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 1, Method 2)

A solution of benzenesulfonyl chloride (0.579 mL, 4.53 mmol) in DCM (2.0 mL) was added to tert-butyl 4-[4-amino-3-(ethylamino)phenyl]-1,4-diazepane-1-carboxylate (0.605 g, 1.81 mmol), and pyridine (1.02 mL, 12.67 mmol) in DCM (8.0 mL). The mixture was stirred at room temperature for 16 hours and then concentrated. The crude intermediate was purified by column chromatography on silica using CHCl₃/10% MeOH + 0.4% NH₃. Deprotection using HCl-ether/EtOAc gave 0.365 g of the crude product as a HCl-salt. Purification on a reversed phase preparative HPLC gave 94 mg of the product as an acetic acid salt which was converted to the HCl salt and recrystallized from MeOH/Ether: yield 64 mg. ¹H NMR (DMSO-*d*6) δ 9.05 (br s, 2H), 8.66 (s, 1H), 7.89-7.85 (m, 2H), 7.75-7.55 (m, 8H), 7.07 (app d, J=9.1 Hz, 1H), 6.71-6.66 (m, 1H), 5.70 (app d, J=3.2 Hz, 1H), 3.50-3.32 (m, partly obscured by HDO signal, 4H), 3.18-3.14 (m, 2H), 3.05-2.90 (m, 2H), 1.90-1.81 (m, 2H), 0.67 (tr, J=7.2 Hz, 3H); Ms (posES-FIA) *m/z* 515 (M+H)

Method 4 (Scheme 2)

Diverse sulfonylchlorides were added to a solution of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and pyridine (135 μ L, 1.7 mmol) in DCM (7mL). After 1 h at r.t. the solvent was removed. Purification by column chromatography (CH₂Cl₂/MeOH/Heptane, 4:1:15) followed by Boc-deprotection which was achieved by dissolving the residue in small amount of MeOH and adding HCl/ether. The mixture was left at r.t. for 0.5 h after which the solvent was removed. Recrystallization (MeOH/ether) afforded the final product.

EXAMPLE 30

10

N-{5-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide (Scheme 2, Method 4)

N-{5-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.075 g, 0.16 mmol) and , methanesulfonyl chloride (0.017 mL, 0.22 mmole) to give 41.6 mg of a light purple solid; Anal. (C₂₄H₂₇ClN₄O₃S x 1.3H₂O) C, H, N, S.; M⁺ 425.4 Calcd 425.12.

EXAMPLE 31

20

N-{5-(1,4-diazepan-1-yl)-2-[(ethylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 4)

N-{5-(1,4-diazepan-1-yl)-2-[(ethylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.085 g, 0.19 mmol) and ethanesulfonyl chloride (0.032 μ L, 0.25 mmol) to give 29.1 mg of a light purple solid; Anal. (C₂₄H₂₇ClN₄O₃S x 0.75H₂O) C, H, N, S.; M⁺ 439.4 Calcd 439.14.

EXAMPLE 32

30

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}[1,1'-biphenyl]-4-sulfonamide hydrochloride (Scheme 2, Method 4)

10 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}[1,1'-biphenyl]-4-sulfonamide hydrochloride was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.081 g, 0.18 mmol) and , 1,1'-biphenyl-4-sulfonyl chloride (0.059 g, 0.24 mmol) to give 42.9 mg of a light purple solid; Anal. (C₂₄H₂₇ClN₄O₃S) C, H, N, S.; M+ 563.5 Calcd 563.17.

EXAMPLE 33

10 N-(2,1,3-benzoxadiazol-4-yl)-4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]benzenesulfonamide hydrochloride (Scheme 2, Method 4)

15 N-(2,1,3-benzoxadiazol-4-yl)-4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]benzenesulfonamide hydrochloride was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.072 g, 0.16 mmol) and 2,1,3-benzoxadiazol-4-yl sulfonyl chloride (0.072 g, 0.21 mmol) to give 38.0 mg of a light purple solid; M+1 537.2 Calcd 537.15; ¹HNMR δ 8.21 (d, 1H), 7.80 (d, 1H), 7.68-7.46 (m, 6H), 6.92 (d, 1H), 6.49 (dd, 1H), 6.12 (d, 1H), 3.57 (app t, 2H), 3.34 (app t, 2H), 3.17 (app t, 2H), 3.11 (app t, 2H), 2.03-1.95 (m, 2H).

20
EXAMPLE 34

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride (Scheme 2, Method 4)

25 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide (0.084 g, 0.19 mmol) and , 2-naphthylsulfonyl chloride (0.055 mL, 0.24 mmol) to give 67.8 mg of a light purple solid; Anal. (C₂₄H₂₇ClN₄O₃S) C, H, N, S; M+ 529.2 Calcd 529.12.

30
EXAMPLE 35

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 4)

Benzenesulfonylchloride (0.233 g, 1.8 mmol) was added to a solution of N-{5-(4-t-butylloxycarbonyl-1,4-diazepan-1-yl)-2-amino]phenyl} methanesulfonamide (0.540 g, 1.4 mmol) and pyridine (0.995 mL, 12.6 mmol) in DCM (40 mL). After 2 h at rt the solvent was removed. Purification by column chromatography (DCM/MeOH/heptane 4:1:5) gave 580 mg (79 %) of a light purple solid. Boc-deprotection was carried out by dissolving the compound in small amount of MeOH and adding HCl/ether. The solvent was removed and the product was recrystallized from MeOH/ether. M+1 425.2 Calcd 425.12

EXAMPLE 36

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 4)

MeI (45 μ L, 0.72 mmol) was added to a mixture of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl} benzenesulfonamide (0.189 g, 0.36 mmol) and K_2CO_3 (0.124, 0.90 mmol) in acetone (25 mL). The mixture was stirred at r.t. for 2 h, filtered and the solvent was removed. Column chromatography (DCM/MeOH/Heptane 4:1:15) gave 110 mg of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]-phenyl} benzenesulfonamide and 20 mg of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide. Boc-deprotection was carried out by dissolving the compounds in small amount of MeOH and adding HCl/ether. The solvent was removed and the products were recrystallized from MeOH/ether. N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride M+1 439.2 Calcd 439.14.

EXAMPLE 37

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide hydrochloride (Scheme 2, Method 4)

MeI (45 μ L, 0.72 mmol) was added to a mixture of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide (0.189 g, 0.36 mmol) and K_2CO_3 (0.124, 0.90 mmol) in acetone (25 mL). The mixture was stirred at r.t. for 2 h, filtered and the solvent was removed. Purification by column chromatography (DCM/MeOH/Heptane 4:1:15) gave 110 mg of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide and 20 mg of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide. Boc-deprotection was carried out by dissolving the compounds in small amount of MeOH and adding HCl/ether. The solvent was removed and the products were recrystallized from MeOH/ether. N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide hydrochloride M+1 439.2 Calcd 439.14.

15 EXAMPLE 38

N-{4-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride (Scheme 2, Method 4)

MeI (45 μ L, 0.72 mmol) was added to a mixture of N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide (0.189 g, 0.36 mmol) and K_2CO_3 (0.124, 0.90 mmol) in acetone (25 mL). The mixture was stirred at r.t. for 2 h, filtered and the solvent was removed. Purification by column chromatography (DCM/MeOH/heptane 4:1:15) gave N-{4-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)-amino]phenyl}benzenesulfonamide as a colourless oil. Boc-deprotection was carried out by dissolving the compound in small amount of MeOH and adding HCl/ether. The solvent was removed and the residue was recrystallized from MeOH/ether to give 62.7 mg of product M+1 501.3 Calcd 501.16.

Scheme 3

30 To a solution of N-(2-amino-5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-phenyl}

vO

methanesulfonamide (134 mg, 0.35 mmol) and pyridine (250 μ L, 3.14 mmole) in DCM (7mL), the sulfonylchloride (0.455 mmol) was added. After 2 h at r.t. the solvent was removed. Purification by column chromatography (CH₂Cl₂/MeOH/Heptane, 4:1:15) followed by Boc-deprotection which was achieved by dissolving the residue in small amount of 5 MeOH and adding HCl/ether. The mixture was left at r.t. for 0.5 h after which the solvent was removed. Recrystallization (MeOH/ether) afforded the final product.

EXAMPLE 39

10 **N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-1-naphthalenesul-fonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 1-naphthalenesulfonylchloride (103 mg, 0.455 mmol) to give before Boc-deprotection 150 mg of a purple solid. M+1 475.1 Calcd 15 474.14.

EXAMPLE 40

20 **N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-naphthalenesul-fonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 2-naphthalenesulfonylchloride (103 mg, 0.455 mmol) to give before Boc-deprotection 120 mg of a purple solid. M+1 475.1 Calcd 474.14.

25

EXAMPLE 41

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-fluorobenzenesul-fonamide hydrochloride (Scheme 3)

30 The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 4-fluorobenzenesulfonylchloride (89 mg,

0.455 mmol) to give before Boc-deprotection 170 mg of a purple solid. M+1 443.1 Calcd 443.11.

EXAMPLE 42

5

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-nitrobenzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 4-nitrobenzenesulfonylchloride (101 mg, 0.455 mmol) according to general method 3 to give before Boc-deprotection 118 mg of a purple solid. M+1 470.1 Calcd 470.11.

EXAMPLE 43

15 **N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-(trifluoromethyl)-benzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 3-trifluoromethylbenzenesulfonylchloride (111 mg, 0.455 mmol) to give before Boc-deprotection 145 mg of a purple solid. M+1 493.1

20 Calcd 493.11.

EXAMPLE 44

25 **N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and o-toluenesulfonylchloride (87 mg, 0.455 mmol) to give before Boc-deprotection 175 mg of a purple solid. M+1 439.2 Calcd 438.14.

30 EXAMPLE 45

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-(trifluoromethoxy)-benzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 4-trifluoromethoxybenzenesulfonylchloride (119 mg, 0.455 mmol) give 140 mg as a purple solid. M+1 509.1 Calcd 509.11.

EXAMPLE 46

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3,5-dimethyl-4-oxazolesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 3,5-dimethylisoxazole-4-sulfonylchloride (89 mg, 0.455 mmol) 3 to give 120 mg of as purple solid. M+1 444.2 Calcd 444.13.

EXAMPLE 47

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-methoxybenzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} methanesulfonamide and 3-methoxybenzenesulfonylchloride (94 mg, 0.455 mmol) to give 160 mg as a purple solid. M+1 455.2 Calcd 455.13.

INTERMEDIATE 11

25 *tert*-Butyl 4-{4-[(4-methylphenyl)sulfonyl]amino}-3-[(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (scheme 2, Method 4)

tert-Butyl 4-{4-nitro-3-[(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (1 g, 2.4 mmol) was dissolved in THF (20 mL) and methanol (2 mL). Raney nickel (0.2 g) was added followed by hydrazine hydrate (0.2 mL). Nitrogen was evolved and the mixture stirred for 1 hour. The reaction was shown to be incomplete by tlc (CH₂Cl₂, MeOH 9:1) so a further 0.1mL of hydrazine hydrate was added. After a further hour, the reaction mixture

was absorbed onto a bed of silica gel and eluted with CH₂Cl₂:MeOH:NH₄OH (9:1:0.01 150 mL). The solvent was removed by evaporation, toluene (100 mL) was added and evaporated to remove any water and hydrazine. The crude amine (0.9 g) was dissolved in acetonitrile (20 mL). To this solution under nitrogen was added dimethylaminopyridine (0.32 g) and 5 toluenesulfonyl chloride (0.51 g) and the mixture stirred for 3 hours. The solution was poured into water (100 mL) and extracted with ethyl acetate (30 mL). The organic extract was washed with water, dried over MgSO₄ and evaporated to give 0.83 g of crude product which was purified by flash chromatography (EtOAc:Petrol 1:1). Yield 0.53 g (41%) ¹H NMR (400 MHz, CDCl₃) δ 1.38, 1.40 (2s, 9 H), 1.91 (m, *J* = 6.11 Hz, 2 H), 2.44 (s, 3 H), 3.03, 3.05 (2s, 10 3 H), 3.16-3.33 (m, 2 H), 3.46-3.57 (m, 6 H), 6.02 (s, 1 H), 6.21 (ab, *J* = 9.03 Hz, 1 H), 6.30 (ab, *J* = 9.03 Hz, 1 H), 6.97 (d, *J* = 2.69 Hz, 1 H), 7.27 (ab, *J* = 8.55 Hz, 2 H), 7.33, 7.36 (2s, 1 H), 7.57 (ab, *J* = 8.06 Hz, 2 H); MS (ESI+) for C₂₄H₃₄N₄O₆S₂ *m/z* 561.1800 (M+)⁺ (Calculated 561.1817).

15 EXAMPLE 48

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-
methylbenzenesulfonamide hydrochloride (PHA 516123A)
tert-Butyl 4-{4-{{[(4-methylphenyl)sulfonyl]amino}-3-
20 [(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (0.5 g) was dissolved in methanol (15 mL). A solution of HCl in ethyl acetate (1N, 25 mL) was added and the mixture stirred for 2 hours. Ether (200 mL) was added and the mixture stirred for 3 hours to allow full precipitation. The product was collected by filtration, washed with ether and dried. Yield 0.43 g (98%) ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.03 (m, 2 H), 2.36 (s, 3 H), 2.9 (s, 3 H), 3.02-3.09 (br m, 2 H), 3.11-3.19 (br m, 2 H), 3.41 (br t, *J* = 7.08 Hz, 2 H), 3.63 (br m, 2 H), 6.46 (d ab, *J* = 2.8 Hz, 8.8Hz, 1 H), 6.62 (ab, *J* = 8.8 Hz, 1 H), 6.71 (d, *J* = 2.8 Hz, 1 H), 7.36 (ab, *J* = 8.3 Hz, 2 H), 7.58 (ab, *J* = 8.3 Hz, 2 H), 8.39 (s, 1 H), 9.2 (br, 2 H), 9.8 (s, 1 H); MS (ESI+) for C₁₉H₂₇N₄O₄S₂ *m/z* 439.148 (M+H)⁺ (Calculated 439.1474).

30 INTERMEDIATE 12

N-ethyl-N-(5-fluoro-2-nitrophenyl)methanesulfonamide (Scheme 2, Method 4)

N-ethyl-methanesulfonamide (Mijns *et al.* J.Chem.Soc.Chem.Com. 1972 p412) (5 g 40.6 mmol) was added to a suspension of sodium hydride (1.9 g, 55% in mineral oil) in anhydrous DMF (100 mL) under nitrogen. The mixture was warmed to 55°C for one hour 5 and 2,4-difluoronitrobenzene (4.4 mL) was added dropwise. The reaction was stirred at 60°C overnight, poured into water (500 mL) and the product extracted into CH₂Cl₂ (5 x 100mL). The organic extracts were washed with water, dried over MgSO₄ and evaporated to give an oily product. The remaining DMF was removed by trituration with petrol. The crude 10 product was purified by flash chromatography (ethyl acetate:petrol 1:1) to yield the desired product which was recrystallised from ethanol. Yield 3.5g (33%). Calculated N % 10,68 C % 41,22 S % 12,23 H % 4,23; Found N % 10,68 C % 41,39 S % 12,22 H % 4,17.

INTERMEDIATE 13**15 tert-Butyl 4-{3-[ethyl(methylsulfonyl)amino]-4-nitrophenyl}-1,4-diazepane-1-carboxylate (Scheme 2, Method 4)**

N-Ethyl-N-(5-fluoro-2-nitrophenyl)methanesulfonamide (3.2 g, 12.2 mmol), *tert*-butyl 1-homopiperazinecarboxylate (2.5 g) and potassium carbonate (2 g) were heated together in DMSO at 50 °C for 5 hours. The solution was allowed to cool and poured into 20 500 mL of water. The solid product was collected by filtration, washed with water and dried. The product was purified by flash chromatography (ethyl acetate:petrol 1:1). Yield 2.6g (48%) ¹H NMR (400 MHz, CDCl₃) δ 1.16 (t, *J* = 7.33 Hz, 3 H), 1.39 (s, 9 H), 2.0 (br, 2 H), 2.99 (s, 3 H), 3.2 (br, 2 H), 3.54-3.75 (br, 8 H), 6.65 (br d, *J* = 9.3 Hz, 1 H), 6.67 (d, *J* = 2.93 Hz, 1 H), 8.1 (d, *J* = 9.3 Hz, 1 H); MS (ESI+) for C₁₉H₃₀N₄O₆S *m/z* 442 (M⁺).

25

Preparation of N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-sulfonamides

tert-Butyl 4-{3-[ethyl(methylsulfonyl)amino]-4-nitrophenyl}-1,4-diazepane-1-carboxylate (2.5 g, 5.7 mmol) was dissolved in THF (50 mL) and methanol (5 mL). Raney 30 nickel (0.5 g) was added followed by hydrazine hydrate (0.5 mL). Nitrogen was evolved and the mixture stirred for 1 hour. The reaction mixture was absorbed onto a bed of silica gel and

eluted with $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_4\text{OH}$ (9:1:0.01 200 mL). The solvent was removed by evaporation, toluene (200 mL) was added and evaporated to remove any water and hydrazine. The crude amine (2.15 g) was dissolved in acetonitrile (50 mL) with dimethylaminopyridine (0.8 g). This solution was divided into three portions. To each 5 portion was added a sulfonyl chloride (2.2 mmol) and the mixtures were stirred overnight at 40°C. The reactions were worked up by adding to water (150 mL), extracting the product into ethyl acetate, washing with water, drying over MgSO_4 and evaporating. Each of the crude boc protected products was purified by flash chromatography (ethyl acetate:petrol 1:1). They were then deprotected directly by dissolving in methanol (10 mL), 10 adding a solution of HCl in ethyl acetate (1N, 50 mL) and stirring for 2 hours. The products were precipitated with ether (500 mL), collected by filtration and dried under vacuum. The products obtained were:

EXAMPLE 49

15 **N-[4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)-amino]phenyl]-4-methylbenzenesulfonamide hydrochloride (Scheme 2, Method 4)**
Was obtained from toluene sulfonyl chloride: Yield 0.36 g
 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 0.79 (t, $J = 7.08$ Hz, 3 H), 2.04 (m, 2 H), 2.37 (s, 3 H), 20 3.07 (s, 3 H), 3.02-3.12 (br, 2 H), 3.12-3.20 (br, 2 H), 3.45 (t, $J = 5.85$ Hz, 2 H), 3.50 (q, $J = 7.08$ Hz, 2 H), 3.67 (br, 2 H), 6.65-6.73 (m, 2 H), 6.94 (d, $J = 9.03$ Hz, 1 H), 7.38 (ab, $J = 8.06$ Hz, 2 H), 7.70 (ab, $J = 8.06$ Hz, 2 H), 8.52 (s, 1 H), 9.2 (br s, 2 H)
MS (ESI+) for $\text{C}_{21}\text{H}_{30}\text{N}_4\text{O}_4\text{S}_2$ m/z 466.1722 M^+ (Calc 466.1708).

25 **EXAMPLE 50**

N-[4-(1,4-diazepan-1-yl)-2-[ethyl-(methylsulfonyl)-amino]phenyl]-3,4-dimethoxybenzenesulfonamide hydrochloride (Scheme 2, Method 4)

Was obtained from 3,4-dimethoxybenzenesulfonyl chloride: Yield 0.43 g
30 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 0.81 (t, $J = 7.08$ Hz, 3 H), 2.05 (m, 2 H), 3.08 (s, 3 H), 3.03-3.11 (br, 2 H), 3.11-3.19 (br, 2 H), 3.45 (t, $J = 6.10$ Hz, 2 H), 3.52 (q, $J = 7.08$ Hz, 2 H),

3.68 (br t, $J = 5.13$ Hz, 2 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 6.66-6.74 (m, 2 H), 6.97 (d, $J = 8.79$ Hz, 1 H), 7.09 (d, $J = 8.55$ Hz, 1 H), 7.33-7.4 (m, 2 H), 8.49 (s, 1 H), 9.3 (br s, 2 H)
MS (ESI+) for $C_{22}H_{32}N_4O_6S_2$ m/z 512.1759 M^+ (Calc 512.1763).

5 EXAMPLE 51

N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride (Scheme 2, Method 4)

Was obtained from 8-quinoline sulfonyl chloride: Yield 0.46 g

10 1H NMR (400 MHz, DMSO- d_6) δ 0.17 (t, $J = 7.08$ Hz, 3 H), 2.06 (m, 2 H), 2.93 (s, 3 H), 3.0-3.2 (m, 6 H), 3.47 (t, $J = 5.86$ Hz, 2 H), 3.70 (t, $J = 5.12$ Hz, 2 H), 6.59 (m, 1 H), 6.77 (d m, $J = 9$ Hz, 1 H), 7.31 (d, $J = 9$ Hz, 1 H), 7.65-7.75 (m, 2 H), 8.24 (d, $J = 7.32$ Hz, 1 H), 8.29 (d, $J = 9.5$ Hz, 1 H), 8.55 (dd, $J = 8.55, 1.71$ Hz, 1 H), 9 (br, 1 H), 9.09 (dd, $J = 4.16, 1.71$ Hz, 1 H), 9.3 (br, 2 H); MS (ESI+) for $C_{23}H_{29}N_5O_4S_2$ m/z 503.1667 M^+ (Calc 503.1661).

15

INTERMEDIATE 14

N-(5-fluoro-2-nitrophenyl)methanesulfonamide (Scheme 2, Method 4)

2,4-di-Nitrobenzene (5.5mL, 50mmol), methanesulfonamide (4.75g, 50mmol) and 20 potassium carbonate (10g) were stirred together in DMSO (100mL) at 80°C overnight. Water (300mL) was added followed by hydrochloric acid (1N, 300mL). The solid product was collected by filtration, washed with water and dried. Yield 9.57g (82%)

1H NMR (400 MHz, $CDCl_3$) δ 3.2 (s, 3 H), 6.92 (m, 1 H), 7.64 (dd, $J = 10.5, 2.7$ Hz, 1 H), 8.34 (dd, $J = 9.5, 5.6$ Hz, 1 H), 10.0 (brs, 1 H); MS (ESI+) for $C_7H_7FN_2O_4S$ m/z 234 M^+ .

25

INTERMEDIATE 15

N-(5-Fluoro-2-nitrophenyl)-N-methylmethanesulfonamide (Scheme 2, Method 4)

N-(5-fluoro-2-nitrophenyl)methanesulfonamide compound (5g, 21mmol), methyl 30 iodide (3mL) and potassium carbonate (10g) were stirred together in DMSO (100mL) at 80°C overnight. The reaction was not complete and a further 1mL of methyl iodide was

added. After a further 24 hours at 80°C, water (1000mL) was added. The solution was decanted from a small amount of sticky residue. The product crystallized out from the aqueous solution (48 hours) and was collected by filtration, washed with water and dried. Yield 3.3g (63%); ¹H NMR (400 MHz, CDCl₃) δ 3.04 (s, 3 H), 3.30 (s, 3 H), 7.20 (m, 1 H), 7.31 (dd, *J* = 8.54, 2.68 Hz, 1 H), 8.0 (dd, *J* = 9.3, 5.6 Hz, 1 H); MS (ESI+) for C₈H₉FN₂O₄S *m/z* 248 M⁺.

INTERMEDIATE 16

10 **tert-Butyl-4-{3-[methyl(methylsulfonyl)amino]-4-nitrophenyl}-1,4-diazepane-1-carboxylate (Scheme 2, Method 4)**

N-(5-Fluoro-2-nitrophenyl)-N-methylmethanesulfonamide (3.1 g, 12.5 mmol), *tert*-butyl 1-homopiperazinecarboxylate (2.5 g) and potassium carbonate (2 g) were heated together in DMSO (50 mL) at 80 °C overnight. The solution was allowed to cool and poured into 500 mL of water. The solid product was collected by filtration, washed with water and dried. Yield 4.6 g (86%); ¹H NMR (400 MHz, CDCl₃) δ 1.41 (s, 9 H), 2.0 (br s, 2 H), 3.01 (s, 3 H), 3.28 (s, 3 H), 3.3-3.8 (br, 8 H), 6.64 (d, *J* = 8.1 Hz, 1 H), 6.74 (d, *J* = 4.8 Hz, 1 H), 8.09 (d, *J* = 8.1 Hz, 1 H); MS (ESI+) for C₁₈H₂₈N₄O₆S *m/z* 428.1709 (M⁺) (calc. 428.1730).

20 *Preparation of N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-sulfonamides*

tert-Butyl-4-{3-[methyl(methylsulfonyl)amino]-4-nitrophenyl}-1,4-diazepane-1-carboxylate (2.5 g, 5.7 mmol) was dissolved in THF (50 mL) and methanol (5 mL). Raney nickel (0.5 g) was added followed by hydrazine hydrate (0.5 mL). Nitrogen was evolved and the mixture stirred for 1 hour. The reaction mixture was absorbed onto a bed of silica gel and eluted with CH₂Cl₂:MeOH:NH₄OH (9:1:0.01 200 mL). The solvent was removed by evaporation, toluene (200 mL) was added and evaporated to remove any water and hydrazine. The crude amine (2.36 g) was dissolved in acetonitrile (50 mL) with dimethylaminopyridine (0.8 g). This solution was divided into six portions. To three of these portions was added a sulfonyl chloride (1.1 mmol) and the mixtures were stirred overnight at 40°C. The reactions were worked up by adding ethyl acetate (50 mL), washing

with brine and water, drying over $MgSO_4$ and evaporating. Each of the crude BOC protected products was purified by flash chromatography (ethyl acetate:petrol 2:1). They were then deprotected directly by dissolving in methanol (10 mL), adding a solution of HCl in ethyl acetate (1N, 50 mL) and stirring for 2 hours. The products were precipitated with ether (500 mL), collected by filtration and dried under vacuum.

5 The products obtained were:

EXAMPLE 52

10 **N-[4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)-amino]phenyl]-4-methylbenzenesulfonamide hydrochloride (Scheme 2, Method 4)**

Was obtained from toluene sulfonyl chloride: Yield 0.18g

¹H NMR (400 MHz, DMSO-*d*₆) δ 2.04 (br m, 2 H), 2.36 (s, 3 H), 2.72 (s, 3 H), 3.05 (s, 3 H), 3.1-3.4 (m, 4 H), 3.46 (t, *J* = 6.34 Hz, 2 H), 3.70 (t, *J* = 4.88 Hz, 2 H), 6.69 (d, *J* = 2.7 Hz, 1 H), 6.72 (s, 1 H), 6.95 (d, *J* = 8.78 Hz, 1 H), 7.36 (ab, *J* = 8.54 Hz, 2 H), 7.57 (ab, *J* = 8.54 Hz, 2 H), 8.39 (s, 1 H), 9.24 (brs, 2 H); MS (ESI+) for $C_{20}H_{28}N_4O_4S_2$ *m/z* 452.1545 M⁺ (Calc. 452.1552).

EXAMPLE 53

20 **N-[4-(1,4-diazepan-1-yl)-2-[methyl-(methylsulfonyl)amino]phenyl]-naphthalene-2-sulfonamide hydrochloride (Scheme 2, Method 4)**

Was obtained from 2-naphthalenesulfonyl chloride: Yield 0.09g

¹H NMR (400 MHz, DMSO-*d*₆) δ 2.0 (br m, 2 H), 2.66 (s, 3 H), 3.05 (s, 3 H), 3.0-3.4 (m, 4 H), 3.43 (t, *J* = 7.08 Hz, 2 H), 3.66 (br t, *J* = 5.1 Hz, 2 H), 6.65 (dd, *J* = 9.0, 2.9 Hz, 1 H), 6.68 (s, 1 H), 6.90 (d, *J* = 9.0 Hz, 1 H), 7.65 (q, *J* = 8.0 Hz, 1 H), 7.68 (q, *J* = 8.3 Hz, 1 H), 7.8 (d, *J* = 6.8 Hz, 1 H), 8.04 (d, *J* = 7.8 Hz, 1 H), 8.12 (t, *J* = 8.8 Hz, 2 H), 8.32 (s, 1 H), 8.68 (s, 1 H), 9.2 (br, 2 H); MS (ESI+) for $C_{23}H_{28}N_4O_4S_2$ *m/z* 488.1529 M⁺ (Calc. 488.1552).

30 EXAMPLE 54

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-5-(2-pyridinyl)-2-thiophenesulfonamide hydrochloride (Scheme 2, Method 4)

Was obtained from 5-(2-pyridinyl)thiophene-2-sulfonyl chloride: Yield 0.12 g

¹H NMR (400 MHz, DMSO-*d*₆) δ 2.05 (br m, 2 H), 2.90 (s, 3 H), 3.07 (s, 3 H), 3.1-3.4 (m, 4 H), 3.48 (t, *J* = 6.1 Hz, 2 H), 3.71 (m, 2 H), 6.75 (dd, *J* = 9.0, 2.7 Hz, 1 H), 6.78 (s, 1 H), 7.03 (d, *J* = 8.8 Hz, 1 H), 7.39 (dd, *J* = 7.6, 4.2 Hz, 1 H), 7.50 (d, *J* = 4.2 Hz, 1 H), 7.84 (d, *J* = 3.9 Hz, 1 H), 7.91 (td, *J* = 7.6, 1.7 Hz, 1 H), 8.03 (d, *J* = 7.8 Hz, 1 H), 8.56 (d, *J* = 4.9 Hz, 1 H), 8.81 (s, 1 H), 9.3 (br, 2 H); MS (ESI+) for C₂₂H₂₇N₅O₄S₃ *m/z* 521.1200 M⁺ (Calc. 521.1225).

10 **Scheme 3**

To a solution of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl} benzenesulfonamide (92.5 mg, 0.207 mmol) and pyridine (131 μ L, 1.6 mmol) in DCM (7 mL), the sulfonylchloride (0.27 mmol) was added. After 2 h at r.t. the solvent was removed. 15 Purification by columnchromatography (CH₂Cl₂/MeOH/Heptane, 4:1:15) followed by Boc-deprotection which was achieved by dissolving the residue in small amount of MeOH and adding HCl/ether. The mixture was left at r.t. for 0.5 h after which the solvent was removed. Recrystallization (MeOH/ether) afforded the final product.

20 **EXAMPLE 55**

25 **N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride (Scheme 3)**

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 1-naphthalenesulfonylchloride (61 mg, 0.27 mmol) to give 56 mg as purple solid. M+1 537.2 Calcd 537.15; ¹HNMR δ 8.67-8.64 (m, 1H), 8.10 (d, 1H), 8.02-7.98 (m, 1H), 7.89 (dd, 1H), 7.77-7.38 (m, 8H), 6.46 (d, 1H), 6.26 (d, 1H), 30 6.14 (dd, 1H), 3.54 (app t, 2H), 3.36-3.31 (m, 2H), 3.17 (app t, 2H), 2.05-1.96 (m, 2H).

EXAMPLE 56

N-[4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl]-5-(dimethylamino)-1-naphthalenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-[2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl]benzenesulfonamide and dansylchloride (73 mg, 0.27 mmol) to give 51 mg AS purple solid. M+1 580.3 Calcd 580.20; ^1H NMR δ 8.86 (d, 1H), 8.62 (d, 1H), 8.08-7.46 (m, 9H), 6.64 (d, 1H), 6.32 (dd, 1H), 6.14 (d, 1H), 3.53 (app t, 2H), 3.45 (s, 6H), 3.16-3.06 (m, 4H), 2.03-1.95 (m, 2H).

EXAMPLE 57

N-[4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl]-8-quinolinesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-[2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl]benzenesulfonamide and 8-quinolinesulfonylchloride (61 mg, 0.27 mmol) to give 34 mg of a purple solid. M+1 538.2 Calcd 538.15.

EXAMPLE 58

N-[4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl]-2,4,6-trimethylbenzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-[2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl]benzenesulfonamide and 2-mesitylenesulfonylchloride (59 mg, 0.27 mmol) to give 56 mg as purple solid. M+1 529.3 Calcd 529.70; ^1H NMR δ 7.80-7.47 (m, 5H), 6.93 (s br, 2H), 6.64 (d, 1H), 6.46-6.39 (m, 2H), 3.60 (app t, 2H), 3.39 (app t, 2H), 3.21 (app t, 2H), 3.12 (app t, 2H), 2.36 (s, 6H), 2.26 (s, 3H), 2.08-2.00 (m, 2H).

EXAMPLE 59

N-[4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl]-4-methylbenzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-[2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl]benzenesulfonamide and p-toluenesulfonylchloride (51 mg, 0.27

mmol) to give 22 mg as purple solid. M+1 501.3 Calcd 501.15; ^1H NMR δ 7.77-7.26 (m, 9H), 6.54 (d, 1H), 6.50 (d, 1H), 6.40 (dd, 1H), 3.63 (app t, 2H), 3.42 (app t, 2H), 3.25 (app t, 2H), 3.16 (app t, 2H), 2.38 (s, 3H), 2.11-2.03 (m, 2H).

5 EXAMPLE 60

N-[5-(1,4-diazepan-1-yl)-2-({{(E)-2-phenylethenyl}sulfonyl}amino)phenyl]benzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and beta-styrenesulfonylchloride (55 mg, 0.27 mmol) to give before Boc-deprotection 12 mg as purple solid. M+1 513.6 Calcd 512.15; ^1H NMR δ 7.78-7.38 (m, 10H), 7.20 (d, 1H), J = 15.4 Hz, 7.10 (d, 1H), 6.98 (d, 1H), J = 15.4 Hz, 6.56 (dd, 1H), 6.44 (d, 1H), 3.62 (app t, 2H), 3.41 (app t, 2H), 3.23 (app t, 2H), 3.15 (app t, 2H), 2.09-2.01 (m, 2H).

15

EXAMPLE 61

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,5-dimethoxybenzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)-phenyl}benzenesulfonamide and 2,5-dimethoxybenzenesulfonylchloride (64 mg, 0.27 mmol) to give 14 mg as purple solid. M+1 547.3 Calcd 547.16; ^1H NMR δ 7.71-7.00 (m, 9H), 6.48 (dd, 1H), 6.16 (d, 1H), 4.04 (s, 3H), 3.68 (s, 3H), 3.56 (app t, 2H), 3.33 (app t, 2H), 3.17 (app t, 2H), 3.11 (app t, 2H), 2.03-1.95 (m, 2H).

25

EXAMPLE 62

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride (Scheme 3)

30 The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and o-toluenesulfonylchloride (51 mg, 0.269

mmol) to give 18 mg as purple solid. M+1 501.3 Calcd 501.15; ^1H NMR δ 7.78-7.17 (m, 9H), 6.68-6.35 (m, 3H), 3.63-3.10 (m, 8H), 2.59 (s, 3H), 2.09-2.01 (m, 2H).

EXAMPLE 63

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4-Butoxy-N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-benzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 4-n-butoxybenzenesulfonylchloride (67 mg, 0.269 mmol) to give 27 mg as purple solid. M+1 559.4 Calcd 559.20; ^1H NMR δ 7.77-7.47 (m, 7H), 6.96-6.93 (m, 2H), 6.55 (d, 1H), 6.52 (d, 1H), 6.41 (d, 1H), 4.01 (t, 2H), 3.63 (app t, 2H), 3.43 (app t, 2H), 3.25 (app t, 2H), 3.17 (app t, 2H), 2.11-2.03 (m, 2H), 1.80-1.71 (m, 2H), 1.53-1.45 (m, 2H), 0.98 (t, 3H).

15 EXAMPLE 64

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 3,5-dimethylisoxazolesulfonylchloride (53 mg, 0.269 mmol) to give 32 mg as purple solid. M+1 506.3 Calcd 506.15; ^1H NMR δ 7.75-7.48 (m, 5H), 6.92 (d, 1H), 6.59 (dd, 1H), 6.28 (d, 1H), 3.62 (app t, 2H), 3.41 (app t, 2H), 3.21 (app t, 2H), 3.12 (app t, 2H), 2.23 (s, 3H), 2.13 (s, 3H), 2.09-2.01 (m, 2H).

25 EXAMPLE 65

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-fluoro-2-methylbenzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 5-fluoro-2-methylbenzenesulfonylchloride (56 mg, 0.269 mmole) to give 7 mg as purple solid. M+1 519.3 Calcd 519.15; ^1H NMR δ

7.78-7.18 (m, 8H), 6.72 (d, 1H), 6.45 (dd, 1H), 6.34 (d, 1H), 3.59 (app t, 2H), 3.38 (app t, 2H), 3.21 (app t, 2H), 3.13 (app t, 2H), 2.57 (s, 3H), 2.06-1.98 (m, 2H).

EXAMPLE 66

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N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-(methylsulfonyl)benzenesulfonamide hydrochloride (Scheme 3)

The compound was synthesized from of N-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}benzenesulfonamide and 4-methylsulfonylbenzenesulfonylchloride (69 mg, 0.269 mmole) to give 38 mg as purple solid. M+1 565.3 Calcd 565.12; ¹HNMR δ 8.08-7.48 (m, 9H), 6.76 (d, 1H), 6.48 (dd, 1H), 6.32 (d, 1H), 3.61 (app t, 2H), 3.38 (app t, 2H), 3.21 (app t, 2H), 3.17 (app t, 2H), 3.14 (app t, 2H), 2.08-2.00 (m, 2H).

EXAMPLE 67

15

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide (Scheme 3)

N-methyl- {2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}-benzenesulfonamide (0.196 g, 0.426 mmol) was dissolved in pyridine (1.67 ml) followed by the addition of methyl sulphonylchloride (57 mg, 0.50 mmol) The ractiom was stirred at rt for 3 h. The mixture was concentrated and treated with trifluoroacetic acid (50%) in DCM for 30 min then concentrated and left for our HPLC Separation specialists. Further purification by column cheomatography DCM/ MeOH (9:1) afforded 32 mg, 0.058 mmol in 13% yield of the title compound. ¹H NMR (CD₃OD) δ 2.17 (m, 2 H), 3.05 (s, 3 H), 3.14 (s, 3 H), 3.27 (m, 2 H), 3.38 (m, 2 H), 3.57 (m, 2 H), 3.77 (m, 2 H), 6.28 (d, 1 H), 6.41 (dd, 1 H), 7.06 (d, 1 H), 7.65 (m, 5 H); ¹³C NMR (CD₃OD) δ 25.0, 38.7, 39.0, 45.1, 45.5, 45.8, 47.0, 100, 103.9, 108.1, 121.4, 125, 126, 128, 133.4, 136, 137.5, 148.5; M/Z Calc for (C₁₉H₂₆N₄O₄S₂) 438.14 found M⁺+1=439.2

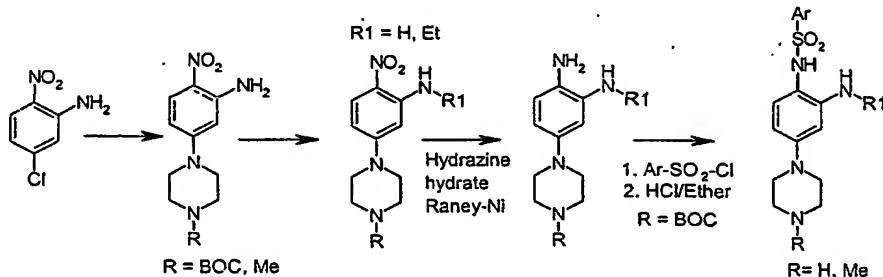
30 EXAMPLE 68

N-[5-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl]-4-methylbenzenesulfonamide (Scheme 3)

N-methyl-{2-amino-5-(4-*t*-butyloxycarbonyl-1,4-diazepan-1-yl)- phenyl}-benzenesulfonamide (0.196 g, 0.426 mmol) was dissolved in pyridine (1.67 ml) followed by 5 the addition of p-methylphenyl-sulphonylchloride (88 mg, 0.50 mmol) the reaction was stirred at rt for 3h. The mixture was concentrated and treated with trifluoroacetic acid (50%) in DCM for 30 min then concentrated and left for our HPLC Separation specialists. Further purification by flash column chromatography DCM / MeOH (9:1) afforded 0.110 g, 0.175 mmol in 40% yield of title compound. ^1H NMR (CD₃OD) δ 2.17 (m, 2 H), 2.52, (s, 3H), 3.0-10 3.4 (m; 7 H), 3.52 (m, 2 H), 3.74 (m, 2 H), 6.15 (d, 1 H), 6.41 (d, 1 H), 6.92 (s, 1 H), 7.5-7.80 (m, 6 H); M/Z Calc for (C₂₅H₃₀N₄O₄S₂) 514.1708 found M⁺ 514.1708.

General method for the preparation of monosulfonamides

15 **Scheme 4**



EXAMPLE 69

20

N-[2-Amino-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide (Scheme 4)

tert-Butyl 4-(3-amino-4-nitrophenyl)-1-piperazinecarboxylate (1.5 g, 3.5 mmol) was dissolved in methanol:THF (4:1). Raney-Ni (900 mg) was added followed by addition of hydrazine monohydrate (900 mg). The reaction was stirred at r. t. under N₂ atmosphere 25 overnight. Starting material was present. Raney-Ni (400 mg) was added and the reaction was stirred overnight. The reaction was filtered through celite pad followed by washings with

ethanol. The volatiles were evaporated to afford 93% of 2-amino-5-(4-t-butyloxycarbonyl-1-piperazinyl) aniline.

2-amino-5-(4-t-butyloxycarbonyl-1-piperazinyl) aniline (150 mg, 0.382 mmol) was dissolved in CH_2Cl_2 (2 mL). 3-fluorophenylsulfonylchloride (74 mg, 0.382 mmol), pyridine (215 μL , 2.67 mmol) were added and the reaction was stirred at room temperature for 2 hr. The reaction was quenched with NaHCO_3 (saturated aqueous solution), extracted with CH_2Cl_2 . The organic phase was dried (MgSO_4), filtered and concentrated to give an oil residue that was purified by flash column chromatography (SiO_2 , $\text{CH}_3\text{Cl}:\text{MeOH}:\text{NH}_3$ 9:1:0.4%) to afford of N-[2-amino-4-(4-tert-butyloxycarbonyl-1-piperazinyl)-3-fluorobenzenesulfonamide (80 %).

N-[2-amino-4-(4-tert-butyloxycarbonyl-1-piperazinyl)-3-fluorobenzenesulfonamide (110 mg) were dissolved in methanol (0.5 mL) followed by the addition of diethylether (2 mL). Ether/HCl gas was added till pH = 1. The reaction was stirred at room temperature for 5 h to afford the title product as a white solid ^1H NMR (methanol-d3) δ 3.25-3.50 (m, 8H); 6.5 (d, 1H); 6.75 (dd, 1H), 7.0 (bs, 1H); 7.3-7.6 (m, 4H); MS (posEI-DIP) m/z = 351.2 ($\text{M}+\text{H}$).

EXAMPLE 70

N-[2-(ethylamino)-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride (Scheme 4)

To a solution of N-2-ethyl-4-(4-methyl-1-piperazinyl)-1,2-benzenediamine (0.200 g, 0.853 mmol) and pyridine (0.48 mL, 5.97 mmol) in DCM (8 mL) was added a solution of 3-fluorobenzenesulfonyl chloride (249 mg, 1.28 mmol) in DCM (2 mL). The mixture was stirred at room temperature for 16 hours. DCM (10 mL) was added and the mixture was washed with saturated aqueous NaHCO_3 . The organic layer was dried over Na_2SO_4 , filtered and concentrated. Column chromatography on Al_2O_3 using $\text{EtOAc}/5\%$ MeOH as eluent gave two products. First fraction contains 110 mg of N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride. Second fraction contains 100 mg of N-[2-

(ethylamino)-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride. Both products were converted to the HCl-salts. N-[2-(ethylamino)-4-(4-methyl-1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide hydrochloride: ^1H NMR (DMSO-*d*6) δ 11.24 (br s, 1H), 9.76 (br s, 1H), 7.66-7.59 (m, 1H), 7.56-7.50 (m, 3 H), 6.62 (app d, J =8.8 Hz, 1H), 6.55-6.35 (m, 2H), 3.80-3.70 (m, 2 H), 3.46-3.40 (m, 2H), 3.15-2.96 (m, 6H), 2.76 (app d, J =4.4 Hz, 3H), 1.08 (tr, J =7.2 Hz, 3H); ^{13}C NMR (CD₃OD) δ 161.03 (d, J_{CF} =248 Hz), 149.32, 142.13 (d, J_{CF} =6.4 Hz), 140.72, 131.43 (d, J_{CF} =7.4 Hz), 128.56, 123.22, 119.93 (d, J_{CF} =20 Hz), 115.91, 113.86 (d, J_{CF} =24 Hz), 107.78, 103.12, 51.83, 45.04, 41.80, 40.62, 12.88; AccMs (posES-FIA) found: 392.1672, calc: 392.1782; Ms (posES-FIA) *m/z* 393 (M+H).

EXAMPLE 71

4-Chloro-N-[5-(4-methyl-1,4-diazepan-1-yl)-2-nitrophenyl]benzenesulfonamide (Scheme 4)

4-chlorobenzene sulfonamide (3.5 g, 18.3 mmol) was added slowly to a suspension of sodium hydride (1.6 g, 55% suspension in mineral oil, 36.6 mmol) in anhydrous DMF (50 mL) under an atmosphere of nitrogen. The mixture was warmed to 40°C for 1 hour and 2,4-difluoronitrobenzene (2 mL) was added dropwise. This mixture was stirred at 60°C overnight. The cooled reaction mixture was poured into hydrochloric acid (1 N, 250 mL) and extracted with ethyl acetate (2 x 50 mL). The organic extracts were washed with water, dried over MgSO₄ and evaporated to give a yellow solid. The product was re-crystallized from ethanol. Yield 2.4g (40%). ^1H NMR (400 MHz, CDCl₃) δ 6.85 (m, 1 H), 7.48 (AB, J = 8.3 Hz, 2 H), 7.56 (dd, J = 10.01, 2.68 Hz, 1 H), 7.84 (AB, J = 8.3 Hz, 2 H), 8.21 (dd, J = 9.28, 5.61 Hz, 1 H), 10 (bs, 1 H). Calculated N 8.47%, C 43.58%, S 9.70%, H 2.44%; Found N 8.54%, C 43.89%, S 10.10%, H 2.76%. 4-Chloro-N-[5-fluoro-2-nitrophenyl]benzenesulfonamide (1g, 3mmol) and N-methylhomopiperazine (0.4mL) were heated together at 130 °C for 3 hours. The product was allowed to cool, dissolved in CH₂Cl₂ (50 mL) and washed with aqueous sodium bicarbonate. The organic phase was dried over MgSO₄ and evaporated to give 1.05 g of a yellow solid which was re-crystallized from toluene. Yield 0.65g (51%). ^1H NMR (400 MHz, CDCl₃) δ 1.98 (q, J = 5.62 Hz, 1 H), 2.37

(s, 3 H), 2.52 (t, J = 5.62 Hz, 2 H), 2.67 (t, J = 5.12 Hz, 2 H), 3.55 (t, J = 6.35 Hz, 2 H), 3.60 (t, J = 5.12 Hz, 2 H), 6.34 (dd, J = 9.77, 2.68 Hz, 1 H), 6.86 (d, J = 2.68 Hz, 1 H), 7.43 (ab, J = 8.79 Hz, 2 H), 7.79 (ab, J = 8.79 Hz, 2 H), 8.01 (d, J = 9.77 Hz, 1 H), 11.6 (br s, 1 H).
Calculated N 13.19%, C 50.88%, H 4.98%; Found N 13.27%, C 50.99%, H 4.83%.

5

EXAMPLE 72

N-[2-amino-5-(1,4-diazepan-1-yl)phenyl]benzenesulfonamide (Scheme 4)

N-{5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-nitro-phenyl}benzenesulfonamide (1.85 g, 3.88 mmol) was dissolved in EtOH/THF (1:4). Hydrazine (0.970 mL, 19.4 mmol) and Raney-Ni (0.180 g) was added. After 1 h at room temperature, the reaction was filtered through wet celite and the solvent was removed to afford 1.71 g of colorless oil. Boc-deprotection was achieved by dissolving N-{5-(4-t-butyloxycarbonyl-1,4-diazepan-1-yl)-2-amino-phenyl}benzenesulfonamide (0.039 g) in small amount of MeOH and adding HCl/ether. The mixture was left at room temperature for 0.5 h after which the solvent was removed. Re-crystallization from MeOH/ether gave PHA-509592A (23 mg) as a white solid. M+1 347.4 Calcd 347.15; $^1\text{H-NMR}$ δ 7.73-7.54 (m, 5H), 7.30 (d, 1H), 6.84 (dd, 1H), 5.78 (d, 1H), 3.55 (app t, 2H), 3.32-3.26 (m, 2H), 3.13-3.08 (m, 4H), 2.03-1.92 (m, 2H).

20 EXAMPLE 73

N-[2-amino-5-(4-methyl-1,4-diazepan-1-yl)phenyl]benzenesulfonamide hydrochloride (Scheme 4)

The above sulfonamide (0.6 g, 1.8 mmol) in methanol (50 mL) with Palladium (10% on C, 0.3g) was hydrogenated at atmospheric pressure for one hour during which time 140 mL of hydrogen was consumed. The solution was filtered and evaporated to give colorless oil. The oil was dissolved in toluene (20 mL) and treated with a solution of hydrogen chloride in ethyl acetate. The product was triturated with cyclohexane, collected by filtration and dried. Yield 0.44g (73%). A portion was recrystallized from toluene:ethanol 1:1. ^1H NMR (400 MHz, CDCl_3) δ 1.95 (br, 1 H), 2.17 (br, 1 H), 2.72 (s, 3 H), 2.80-3.65 (br m, 8 H), 5.92 (br, 1 H), 6.66 (dd, J = 2.69, 9.03 Hz, 1 H), 7.20 (d, J = 9.03 Hz, 1 H), 7.63 (t, J = 7.81

Hz, 2 H), 7.71 (t, J = 7.32 Hz, 1 H), 7.81 (d, J = 7.32 Hz, 2 H), 9.8 (br, 3 H), 11 (br s, 1 H).

MS (ESI+) for $C_{18}H_{24}N_4O_2S$ m/z 360.1634 (M^+)⁺ (Calculated 360.1620)

EXAMPLE 74

5

N-[4-Nitro-3-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 4)

A mixture of difluoronitrobenzene (1.31 g, 8.21 mmol), Boc-piperazine (1.84 g, 9.8 mmol) and K_2CO_3 in DMF was stirred at room temperature overnight. The mixture was filtered and the DMF was removed. The residue was dissolved in CH_2Cl_2 and extracted with 10 HCl (1M) three times. The organic layers were dried ($MgSO_4$), filtered and the solvent was removed. Purification by column chromatography (SiO_2 , $CH_2Cl_2/heptane$, 1:4) gave 1.14 g of yellow solid. 1H -NMR δ 7.90 (dd, 1H), 6.77-6.69 (m, 2H), 3.60-3.57 (m, 4H), 3.03-3.00 (m, 4H), 1.46 (s, 9H); MS (posEI-DIP) m/z = Found: 348.2 ($M^+ + Na^+$). NaH (17.2 mg, 0.43 mmol) was added to a solution of 4-(2-nitro-5-fluorophenyl)-1-(*t*-
15 butyloxycarbonyl)piperazine (0.079 g, 0.215 mmol) and benzenesulfonamide (0.044g, 0.280 mmol) in DMF. The mixture was heated at 80°C over night and filtered. Purification by column chromatography (SiO_2 , $CH_2Cl_2/heptane$, 1:4) gave 0.075 g of N-[2-nitro-4-(*t*-
butyloxycarbonylpiperazinyl)]phenyl]benzenesulfonamide of which 0.025 mg was Boc-
20 deprotected by dissolving the compound in MeOH and adding HCl/ether. The mixture was stirred for 0.5 h after which the solvent was removed. Re-crystallization MeOH/ether gave 24.6 mg of a yellow solid. 1H -NMR δ 7.88 (app d, 3H), 7.63-7.52 (m, 3H), 7.07 (d, 1H), 6.89 (dd, 1H), 3.38-3.34 (m, 4H), 3.25-3.21 (m, 4H); MS (posEI-DIP) m/z = Found: 363.3 ($M^+ + H^+$).

25

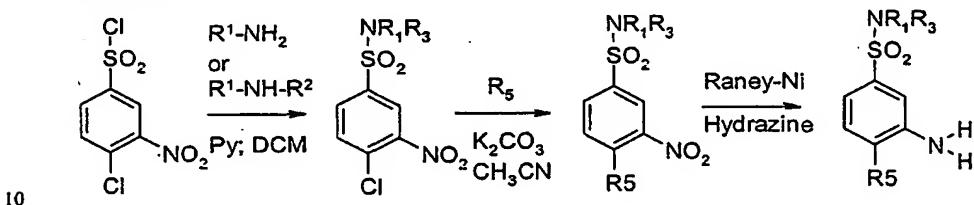
EXAMPLE 75

N-[4-amino-3-(1-piperazinyl)phenyl]benzenesulfonamide hydrochloride (Scheme 4)

To a solution of N-[2-nitro-4-(*t*-butyloxycarbonylpiperazinyl)]phenyl]benzenesulfonamide (50 mg, 0.108 mmol) in THF/EtOH 4:1 was added Raney-Ni (5 mg) and 30 hydrazine hydrate (27 μ L, 0.54 mmol). The mixture was stirred at room temperature for 6 h followed by filtration of the reaction mixture through wet Celite. Removal of the solvent and

purification by column chromatography (SiO₂, CH₂Cl₂/heptane/MeOH, 4:5:1) gave N-[2-amino-4-(t-butyloxycarbonyl-piperazinyl)]phenyl-benzenesulfonamide. Boc-deprotection was achieved by dissolving the compound in MeOH and adding HCl/ether. The mixture was stirred for 0.5 h after which the solvent was removed. Re-crystallization (MeOH/ether) gave 5 a white solid that had to be purified by preparative HPLC to obtain 10 mg of the final product. ¹H-NMR δ 7.66-7.45 (m, 5H), 6.78 (d, 1H), 6.62 (d, 1H), 6.50 (dd, 1H), 3.39-3.35 (m, 4H), 3.02-2.99 (m, 4H); MS (posEI-DIP) m/z = Found: 333.0 (M⁺ + H⁺).

Scheme 5



10

Method 5

4-Chloro-3-nitrobenzenesulfonyl chloride, taken from a prepared stock solution, (1.78 mmol, 1.0 eq) in CH₂Cl₂ (2 mL) was added to a solution of the appropriate Rⁿ-15 substituted anilines (R¹-NH₂ or R¹-NH-R³) (1.62 mmol, 1.0 equiv.) in the presence of pyridine (11.34 mmol, 7.0 equiv.).

The reactions were stirred overnight at room temperature. Each mixture was washed with 1N HCl followed by NaHCO₃ (sat. aqueous). Each organic phase was separated, dried 20 (Na₂SO₄), and filtered. CH₂Cl₂ (2 mL) were added to each reaction mixture followed by the addition of K₂CO₃ (3.24 mmol, 2.0 equiv.) and homopiperazine or other amines of choice (i.e. R⁵) (2.11 mmol, 1.3 equiv.). Each reaction mixture was stirred at room temperature for 2 days. The volatiles were eliminated using a speed vac. Each reaction mixture was dissolved 25 in a 4:1 EtOH:THF (25 mL) followed by addition of Raney-Ni (0.5 mL suspension in EtOH) and hydrazine monohydrate (8.10 mmol, 5.0 equiv.). Each mixture was stirred at room temperature for 2 days and then filtered (Celite pad pretreated with water). The filtrates were concentrated to give the crude products (LC-MS). An aliquot of each reaction mixture was

purified by reversed phase preparative HPLC to give analytical samples which were converted to their HCl-salts and sent for pharmacological testing.

EXAMPLE 76

5

3-Amino-4-(1,4-diazepan-1-yl)-N-(4-methoxyphenyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)

The compound was prepared from p-anisidine; (crude yield 0.238 g, yield analytical pure sample 0.137 g); ^1H NMR (CDCl_3) δ 7.43-7.39 (m, 2H), 7.37-7.33 (m, 1H), 7.00-6.96 (m, 2H), 6.78-6.74 (m, 2H), 3.71 (s, 3H), 3.47-3.38 (m, 6H), 3.17-3.13 (m, 2H), 2.19-2.12 (m, 2H); MS (posESI) m/z = 377 ($\text{M}+\text{H}^+$).

EXAMPLE 77

15 **3-Amino-4-(1,4-diazepan-1-yl)-N-(3-methoxyphenyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

The compound was prepared from m-anisidine; (crude yield 0.546 g, yield analytical pure sample 0.020 g); ^1H NMR (CDCl_3) δ 7.71-7.67 (m, 2H), 7.51-7.47 (m, 1H), 7.12-7.07 (m, 1H), 6.72-6.69 (m, 1H), 6.68-6.65 (m, 1H), 6.63-6.59 (m, 1H), 3.71 (s, 3H), 3.48-3.40 (m, 6H), 3.18-3.14 (m, 2H), 2.21-2.15 (m, 2H); MS (posES-FIA) m/z = 377 ($\text{M}+\text{H}^+$).

EXAMPLE 78

25 **3-Amino-4-(1,4-diazepan-1-yl)-N-(2-methoxyphenyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

The compound was prepared from o-anisidine; (crude yield 0.469 g, yield analytical pure sample 0.010 g); ^1H NMR (CDCl_3) δ 7.51-7.47 (m, 2H), 7.42-7.35 (m, 2H), 7.11-7.06 (m, 1H), 6.89-6.82 (m, 2H), 3.57 (s, 3H), 3.47-3.38 (m, 6H), 3.17-3.12 (m, 2H), 2.20-2.13 (m, 2H); MS (posES-FIA) m/z = 377 ($\text{M}+\text{H}^+$).

30

EXAMPLE 79

3-Amino-4-(1,4-diazepan-1-yl)-N-(3-fluorophenyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)

5 The compound was prepared from 3-fluoroaniline; (crude yield 0.580 g, yield analytical pure sample 0.043 g); ^1H NMR (CD_3OD) δ 7.58-7.49 (m, 2H), 7.41-7.35 (m, 1H), 7.23-7.17 (m, 1H), 6.93-6.87 (m, 2H), 6.79-6.73 (m, 1H), 3.46-3.37 (m, 6H), 3.17-3.13 (m, 2H), 2.20-2.12 (m, 2H); MS (posES-FIA) m/z = 365 ($\text{M}+\text{H}^+$).

10 EXAMPLE 80

3-Amino-4-(1,4-diazepan-1-yl)-N-methyl-N-phenylbenzenesulfonamide hydrochloride (Scheme 5, Method 5)

15 The compound was prepared from N-methylaniline; (crude yield 0.590 g, yield analytical pure sample 0.010 g); ^1H NMR (CD_3OD) δ 7.41-7.36 (m, 1H), 7.35-7.22 (m, 5H), 7.15-7.11 (m, 2H), 3.50-3.44 (m, 6H), 3.23-3.17 (m, 5H), 2.33-2.16 (m, 2H); MS (posEI) m/z = 360 ($\text{M}+\text{H}^+$).

EXAMPLE 81

20

3-Amino-4-(1,4-diazepan-1-yl)-N-(4-isopropylphenyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)

25 The compound was prepared from 4-isopropylaniline; (crude yield 0.600 g, yield analytical pure sample 0.015 g); ^1H NMR (CD_3OD) δ 7.48-7.41 (m, 2H), 7.35-7.31 (m, 1H), 7.10-7.05 (m, 2H), 7.03-6.98 (m, 2H), 3.47-3.35 (m, 6H), 3.17-3.12 (m, 2H), 2.80 (sept, J = 6.8 Hz, 1H), 2.20-2.10 (m, 2H), 1.17 (d, J = 6.8 Hz, 6H); MS (posEI) m/z = 388 ($\text{M}+\text{H}^+$).

EXAMPLE 82

30 **3-Amino-4-(1,4-diazepan-1-yl)-N-(4-methylphenyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)**

EXAMPLE 86

3-Amino-N-(2,4-dichlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide5 **hydrochloride (Scheme 5, Method 5)**

The compound was prepared from 2,4-dichloroaniline; (crude yield 0.446 g, yield analytical pure sample 0.080 g); ^1H NMR (CD_3OD) δ 7.53-7.50 (m, 1H), 7.37-7.35 (m, 1H), 7.32-7.27 (m, 2H), 7.25-7.23 (m, 2H), 3.48-3.37 (m, 6H), 3.18-3.12 (m, 2H), 2.20-2.10 (m, 2H); MS (posEI) m/z = 415 ($\text{M}+\text{H}^+$).

10

EXAMPLE 87

3-Amino-N-(2-methyl-5-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide**hydrochloride (Scheme 5, Method 5)**

15

The compound was prepared from 2-methyl-5-chloroaniline; (crude yield 0.516 g, yield analytical pure sample 0.015 g); ^1H NMR (CD_3OD) δ 7.47-7.34 (m, 3H), 7.16-7.13 (m, 1H), 7.10 (-7.04 (m, 2H), 3.48-3.39 (m, 6H), 3.20-3.15 (m, 2H), 2.21-2.14 (m, 2H); MS (posESI) m/z = 395 ($\text{M}+\text{H}^+$).

20

EXAMPLE 88

3-Amino-N-(2-methyl-3-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide**hydrochloride (Scheme 5, Method 5)**

25

The compound was prepared from 2-methyl-3-chloroaniline; (crude yield 0.537 g, yield analytical pure sample 0.22 g); ^1H NMR (CD_3OD) δ 7.40-7.34 (m, 3H), 7.26-7.23 (m, 1H), 7.08-6.99 (m, 2H), 3.50-3.38 (m, 6H), 3.20-3.16 (m, 2H), 2.21-2.14 (m, 2H) 2.11 (s, 3H); MS (posESI) m/z = 395 ($\text{M}+\text{H}^+$).

EXAMPLE 89

3-Amino-N-(4-trifluoro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)

5 The compound was prepared from 4-trifluoroaniline; (crude yield 0.319 g, yield analytical pure sample 0.013 g); ^1H NMR (CD_3OD) δ 7.53-7.45 (m, 2H), 7.27-7.22 (m, 3H), 7.13-7.08 (m, 2H), 3.43-3.30 (m, partly obscured by solvent signal, 6H), 3.14-3.09 (m, 2H), 2.12-2.06 (m, 2H); MS (posESI) m/z = 415 ($\text{M}+\text{H}^+$).

EXAMPLE 90

10

3-Amino-N-(4-fluorophenyl)-4-(1,4diazepan-1-yl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)

15 The compound was prepared from 4-fluoroaniline; (crude yield 0.700 g, yield analytical pure sample 0.021 g); ^1H NMR (CD_3OD) δ 7.13-7.04 (m, 4H), 7.03-6.98 (m, 1H), 6.97-6.91 (m, 2H), 3.45-3.30 (m, partly obscured by solvent signal, 6H), 3.15-3.09 (m, 2H); MS (posEI) m/z = 365 ($\text{M}+\text{H}^+$).

EXAMPLE 91

20

3-Amino-N-(2-fluorophenyl)-4-(1,4diazepan-1-yl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)

25 The compound was prepared from 2-fluoroaniline; (crude yield 0.646 g, yield analytical pure sample 0.080 g); ^1H NMR (CD_3OD) δ 7.48-7.43 (m, 1H), 7.36-7.34 (m, 1H), 7.36-7.27 (m, 1H), 7.25-7.21 (m, 1H), 7.15-7.05 (m, 2H), 7.02-6.95 (m, 1H), 3.46-3.34 (m, 6H), 3.17-3.12 (m, 2H), 2.16-2.10 (m, 2H) ; MS (posESI) m/z = 365 ($\text{M}+\text{H}^+$).

EXAMPLE 93

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4-(1,4-Diazepan-1-yl)-3-nitro-N-benzenesulfonamide hydrochloride (Scheme 5, Method 5)

4-Chloro-3-nitro-N-benzenesulfonamide (1.52 g, 4.87 mmol), K_2CO_3 (1.01 g, 7.3 mmol) and homopiperazine (0.585 g, 5.8 mmol) in CH_3CN (100 mL) was heated to 70°C for 2h. The mixture was filtered and the solvent was removed. Column chromatography ($CH_2CL_2/MeOH/heptane$ 4:1:5 x 0.2 % NH_3) gave 1.34 g of 4-(1,4-diazepan-1-yl)-3-nitro-N-
5 benzenesulfonamide together with 0.152 g of the dialkylated product. The product (0.040 g) was transferred to its HCl-salt to give 0.038 g of the final product. Anal. ($C_{17}H_{21}ClN_4O_4S$ x 0.5 H_2O) C, H, N.; MS (posESI) m/z = 377.4 ($M+H^+$).

EXAMPLE 94

10 **3-Amino-4-(1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide hydrochloride (Scheme 5, Method 5)**

15 4-(1,4-Diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide (0.599 g, 1.6 mmol) was dissolved in $EtOH/THF$ (1:4). Hydrazine (0.398 mL, 8.0 mmol) and Raney-Ni (0.060 g) were added. After 1 h at room temperature the reaction was filtered through wet celite and the solvent was removed. The product was transferred to its HCl-salt by dissolving it in $MeOH$ and adding HCl/ether. The solvent was removed and re-crystallized from ($MeOH/ether$) to give 0.537 g of a white solid. Anal. ($C_{17}H_{21}ClN_4O_4S$ x 1.5 H_2O) C, H, N.; MS (posESI) m/z = 347.4 ($M+H^+$).

20 EXAMPLE 92

3-Amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide (Scheme 5, Method 5)

25 4-Chloro-3-nitrobenzenesulfonyl chloride (460 mg, 1.8 mmol) was added to a colorless solution of aniline (250 mg, 2.7 mmol) in CH_2Cl_2 (10 mL) followed by pyridine (0.80 mL, 10.0 mmol). The resulting orange solution was stirred at room temperature for 30 minutes, after which time the mixture was concentrated under vacuum. Acidification with 2M aq. HCl followed by extraction using $EtOAc$ and drying with Na_2SO_4 followed by 30 filtration through a plug of silica, gave 500 mg (62%) of 4-chloro-3-nitro-N-phenylbenzenesulfonamide. 1H NMR ($CDCl_3$) δ 8.30 (d, 1H), 7.80 (dd, 2H), 7.55 (d, 1H),

7.20 (m, 5H). MS(negESI) m/z = 311(M- H $^+$). 1-Methylhomopiperazine (258 mg, 2.3 mmol) was added to a solution of 4-chloro-3-nitro-N-phenylbenzenesulfonamide obtained as above (500 mg, 1.6 mmol) in CH₂Cl₂ (20 mL) followed by addition of K₂CO₃ (310 mg, 2.3 mmol). The reaction mixture was heated to reflux. After 2.5 h, the solution was concentrated under 5 vacuum. After adjusting to pH = 6, the product was extracted using EtOAc to give, after drying with Na₂SO₄ and concentration, 450 mg (72%) of 4-(4-methyl-1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide as an orange oil. ¹H NMR (CDCl₃) δ 8.15 (d, 1H), 7.60 (dd, 1H), 7.15 (m), 6.95 (d, 1H), 3.45 (m, 2H), 3.30 (m, 2H), 2.75 (m, 2H), 2.60 (m, 2H), 2.35 (s, 3H), 1.95 (m, 2H). MS (posESI) m/z = 391(M+H $^+$). To a solution of 4-(4-methyl-10 1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide (225 mg, 0.58 mmol) in EtOH/THF (4/1, 25 mL) activated Raney-Ni (slurry in EtOH) and hydrazine monohydrate (142 μ L, 2.9 mmol) were added. After stirring for 30 minutes at room temperature, the mixture was filtered and the yellow solution concentrated to give yellow oil. The oil was dissolved in a mixture diethyl ether/EtOAc followed by addition of excess of HCl/ether. The resulting 15 precipitate was filtered and washed with ether to give, after drying under vacuum at 40°C, 88 mg (38%) of 3-amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide as a beige solid: Mp 84-85°C. MS (posESI) m/z = 361 (M+H $^+$). ¹H NMR (MeOH-d3) δ 7.85 (d, 2H), 7.60 (d, 1H), 7.15 (m, 5H), 3.50 (m, 7H), 3.15 (m, 2H), 3.00 (s, 3H), 2.30 (m, 1H), 2.20 (m, 1H). Anal. (C₁₈H₂₄N₄SO₂.2HCl) C, H, N, S.

20

EXAMPLE 98

3-Amino-N-(3-chlorophenyl)-4-(4-methyl-1-1-piperazinyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)

25 A mixture of 4-chloro-3-nitrobenzenesulfonylchloride (1g, 3.9 mmol), 3-chloroaniline (0.5 mL, 4.7 mmol) and pyridine (1.6 mL) in CH₂Cl₂ (2 mL) was stirred at room temperature. The reaction was quenched with NaHCO₃ (sat aq solution, 30 mL x 3). The organic phase was separated, dried (MgSO₄), and filtered. The volatiles were evaporated and the residue was purified by column chromatography (SiO₂, pentane:EtOAc, 4:1) to give 30 4-chloro-N-(3-chlorophenyl)-3-nitrobenzenesulfonamide; MS (posESI) m/z = 349.2 (M+H $^+$). ¹H NMR (CDCl₃) δ 7.00-7.40 (m, 3H), 7.60-7.90 (m, 3H), 8.70 (bs, 1H). 4-Chloro-N-(3-

chlorophenyl)-3-nitrobenzenesulfonamide (0.45 g, 1.3 mmol), N-methylpiperazine (0.191 mL, 1.73 mmol) and K_2CO_3 (359 mg, 2.6 mmol) in CH_3CN (2.5 mL) as the filtrated was concentrated to give a residue which was purified by column (SiO_2 , $CHCl_3$:MeOH: NH_3 9:1:0.4 %) to give 420 mg of N-(3-chlorophenyl)-4-(4-methyl-1-piperazinyl)-3-nitrobenzenesulfonamide (85 %). Purity >95 % according to HPLC analysis. The compound was dissolved in THF (1 mL) and ethanol (5 mL) was added. The solution was treated with Raney-Ni (50 mg) and hydrazine monohydrate (0.05 mL) overnight. The Raney-Ni was filtered (celite pad), the volatiles were evaporated and the residue was purified by column chromatography (SiO_2 , $CHCl_3$:MeOH: NH_3 9:1:0.4 %). The product was isolated as hydrochloride salt by treatment with HCl gas in diethyl ether to yield 170 mg of final product (32 %).

1H NMR ($DMSO-d_6$) δ 7.25 (appt, 1H), 7.15-7.17 (m, 1H), 7.10-6.12 (m, 1H), 7.00-7.10 (m, 4H); 3.43-3.45 (m, 2H), 3.22-3.24 (m, 4H), 2.96-3.01 (m, 2H), 2.77-2.78 (s, 3H); MS (posESI) m/z = 380.1($M+H^+$).

15

EXAMPLE 99

3-Amino-N-(2-methoxyphenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)

20 The compound was prepared from 4-chloro-3-nitrobenzenesulfonylchloride (1g, 3.9 mmol), 2-methoxyaniline (0.53 mL, 4.7 mmol) and pyridine (1.6 mL) in CH_2Cl_2 (2 mL). 4-Chloro-N-(2-methoxyphenyl)-3-nitrobenzenesulfonamide (0.345 mg) was reacted with N-methylpiperazine (0.144 mL) to afford N-(2-methoxyphenyl)-4-(4-methyl-1-piperazinyl)-3-nitrobenzenesulfonamide which was treated with Raney-Ni and hydrazine monohydrate. The 25 final product was isolated as its HCl salt 1H NMR ($DMSO-d_6$) δ 7.185 (dd, 1H), 7.08 (dt, 1H), 6.975 (d, 1H), 6.91-6.94 (m, 2H); 6.84 (dt, 1H), 3.56 (s, 3H), 3.42-3.47 (m, 2H), 3.22-3.24 (m, 2H), 2.95 (bt, 2H), 2.79 (bs, 3H); MS (posESI) m/z = 376.2 ($M+H^+$).

EXAMPLE 100

30

3-Amino-N-(2-methoxyphenyl)-4-(1-piperazinyl)benzenesulfonamide hydrochloride (Scheme 5, Method 5)

The compound was prepared from 4-chloro-3-nitrobenzenesulfonyl chloride (1 g, 3.9 mmol), 2-methoxyaniline (0.53 mL, 4.7 mmol) and pyridine (1.6 mL) in CH_2Cl_2 (2 mL). 4-
5 Chloro-N-(2-methoxyphenyl)-3-nitrobenzenesulfonamide (0.345 g) was reacted with
piperazine (0.111 g) to afford N-(2-methoxyphenyl)-4-(piperazinyl)-3-
nitrobenzenesulfonamide. This was then treated with Raney-Ni and hydrazine monohydrate.
The final product was isolated as its HCl salt. ^1H NMR ($\text{DMSO}-d_6$) δ 7.18-7.20 (m, 1H),
7.08-7.10 (m, 2H), 6.93-6.96 (m, 1H), 6.91-6.93 (m, 2H); 6.84 (dt, 1H), 3.56 (s, 3H), 3.22-
10 3.27 (m, 4H), 3.00-3.02 (m, 4H); MS (posESI) m/z = 362.1 ($\text{M}+\text{H}^+$).

EXAMPLE 95

2-(1,4-diazepan-1-yl)-5-(4-morpholinylsulfonyl)aniline hydrochloride (Scheme 5, 15 Method 5)

A suspension of homopiperazine (0.196 g, 1.95 mmol), 4-[(4-chloro-3-
nitrophenyl)sulfonyl]morpholine (0.461 g, 1.50 mmol) and K_2CO_3 (0.415 g, 3.00 mmol) in
 CH_3CN (10 mL) was stirred at 65 °C for 16 h. CH_2Cl_2 (10 mL) was added and the mixture
was filtered and concentrated. The crude product was purified by column chromatography on
20 silica using $\text{CHCl}_3 \rightarrow \text{CHCl}_3/10\% \text{ MeOH} + 0.4\% \text{ aqueous ammonia}$ to yield 0.546 g of the
product as a yellow solid (yield 98%); ^1H NMR (CDCl_3) δ 8.13-8.07 (m, 1H), 7.70-7.64 (m,
1H), 7.16-7.12 (m, 1H), 3.78-3.73 (m, 4H), 3.55-3.49 (m, 2H), 3.44-3.36 (m, 2H), 3.19-3.13
(m, 2H), 3.06-3.00 (m, 6H), 2.05-1.95 (m, 2H); ^{13}C NMR (CDCl_3) δ 147.88, 137.39, 131.60,
127.81, 122.66, 118.02, 66.23, 54.45, 51.02, 49.30, 48.27, 46.16, 29.46; MS (posES-FIA)
25 m/z = 372 ($\text{M}+\text{H}^+$). To a solution of 1-[4-(4-morpholinylsulfonyl)-2-nitrophenyl]-1,4-
diazepane (0.445 g, 1.20 mmol) in 30 mL of a 4:1 EtOH:THF solvent system was added
Raney-Ni (100 mg suspension in EtOH) followed by hydrazine monohydrate (300 mg, 6.00
mmol). The mixture was stirred vigorously for 4 h and then filtered through celite that was
pretreated with water. The filtrate was concentrated, and then re-dissolved in CH_3CN ,
30 concentrated again and finally toluene was added and the mixture concentrated once more to
give a brown solid. The crude product was purified by column chromatography (SiO_2 ,

CHCl₃/MeOH/NH₃ 9:1:0.4%) to give 0.365g (yield 89%) of the pure product as a solid. The free base was converted to its HCl salt; ¹H NMR (DMSO-*d*6) δ 9.34 (s, 2H), 7.23-7.16 (m, 2H), 7.04-6.98 (m, 1H), 3.65-3.60 (m, 4H), 3.35-3.20 (m, 6H), 3.11-3.04 (m, 2H), 2.86-2.80 (m, 4H), 2.09-1.99 (m, 2H); MS (posESI) m/z = 341 (M+H⁺).

5

INTERMEDIATE 17

4-Chloro-N-(2-methoxy-phenyl)-3-nitrobenzenesulfonamide (Scheme 5, Method 5)

4-Chloro-3-nitrobenzenesulfonamide (1.73 g, 6.78 mmol) was dissolved in CH₂Cl₂ (7.0 mL). *o*-Anisidine (1.00 g, 8.13 mmol) was added dropwise at room temperature, followed by a slow addition of pyridine (2.0 mL). After 16 h of continued stirring, the reaction mixture was diluted with EtOAc (50 mL) and washed with 1 M HCl (3 x 50 mL). The organic phase was dried (MgSO₄) filtered and evaporated to a brown solid, upon which re-crystallization from ethanol/water gave 2.22 g (95%) of the product as white crystals. ¹H NMR (CDCl₃) δ 8.20 (s, 1H), 7.80 (dd, 1H), 7.56 (d, 1H), 7.53 (d, 1H), 7.13 (t, 1H), 6.96 (t, 1H), 6.76 (d, 1H), 3.66 (s, 3H). The sulfonamide proton was not observed.

INTERMEDIATE 18

20 4-Chloro-3-nitro-N-phenyl-benzenesulfonamide (Scheme 5, Method 5)

Two portions of 4-Chloro-3-nitrobenzenesulfonamide (1.73 g, 6.78 mmol) were dissolved in CH₂Cl₂ (7.0 mL) in reaction flasks. Aniline (757 mg, 8.13 mmol) was added drop-wise at room temperature, followed by slow additions of pyridine (2.0 mL). After 16 h of continued stirring, the reaction mixtures were diluted with ethyl acetate (50 mL) and washed with 1 M HCl (3x50 mL). The organic phases were dried (MgSO₄) and evaporated to brown solids, which upon re-crystallization from ethanol/water gave off-white solid of the product 2.04 g (96%): ¹H NMR (CDCl₃, 400 MHz) δ 8.24 (d, 1H), 7.80 (dd, 1H), 7.61 (d, 1H), 7.30 (t, 2H), 7.20 (t, 1H), 7.09 (d, 2H), 6.79 (bs, 1H); MS (CI) 310.8 (M - H)⁻; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >98%.

25
30

General procedure for reactions between 4-Chloro-3-nitro-N-aryl-benzenesulfonamides and amines (R⁵) (Scheme 5, Method 5)

Solutions of Intermediate 17 (343 mg, 1.00 mmol) and Intermediate 12 (313 mg, 1.00 mmol) in CH₃CN (5 mL) were treated with K₂CO₃ (276 mg, 2.00 mmol) and amines (R⁵) (1.30 mmol) and heated to 80°C for 16 h. The reaction mixtures were diluted with ethyl acetate (50 mL), washed with saturated Na₂CO₃ (3x50 mL), dried (Na₂SO₄) and evaporated to products that could be used for the next step without purification.

INTERMEDIATE 19

10

N-(2-Methoxyphenyl)-4-(3-methyl-piperazin-1-yl)-3-nitrobenzenesulfonamide (Scheme 5, Method 5)

A solution of Intermediate 17 (343 mg, 1.00 mmol) and K₂CO₃ (276 mg, 2.00 mmol) in CH₃CN (5 mL) was treated with 2-methylpiperazine (130 mg, 1.30 mmol). After 16 h of stirring at 80°C, the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated Na₂CO₃ (aq) (3x50 mL). The organic phases were dried (Na₂SO₄) and evaporated to give 398 mg of a yellow foam of the title compound (98%). ¹H NMR (CDCl₃) δ 8.16 (d, 1H), 7.70 (dd, 1H), 7.50 (d, 1H), 7.06 (t, 1H), 6.97 (d, 1H), 6.91 (t, 1H), 6.75 (d, 1H), 3.69 (s, 3H), 2.92-3.17 (m, 6H), 2.61 (t, 1H), 1.05 (d, 3H). The sulfonamide and amine protons were not observed.

INTERMEDIATE 20

4-(Hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-(2-methoxyphenyl)-3-nitrobenzenesulfonamide (Scheme 5, Method 5)

A solution of Intermediate 17 (343 mg, 1.00 mmol) and K₂CO₃ (276 mg, 2.00 mmol) in CH₃CN (5 mL) was treated with octahydropyrrolo[1,2-a]pyrazine (164 mg, 1.30 mmol). After 16 h of stirring at 80 °C, the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated Na₂CO₃ (3 x 50 mL). The organic phases were dried (Na₂SO₄) and evaporated to give 407 mg a yellow foam of the title compound (94%). ¹H NMR (CDCl₃) δ 8.16 (s, 1H), 7.70 (dd, 1H), 7.50 (d, 1H), 7.06 (t, 1H), 7.00 (d, 1H), 6.91 (t, 1H), 6.75 (d, 1H),

4-(Hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-3-nitro-N -phenyl-benzenesulfonamide
(Scheme 5, Method 5)

The compound was prepared from Intermediate 18 and hexahydro-pyrrolo[1,2-a]2-pyrazine 372 mg orange foam (92%): ^1H NMR (CDCl_3 , 400 MHz) δ 8.16 (s, 1H), 7.67 (d, 1H), 7.27 (t, 2H), 7.14 (t, 1H), 7.08 (d, 2H), 7.03 (d, 1H), 3.02-3.35 (m, 5H), 2.83 (dd, 1H), 2.41 (t, 1H), 2.18-2.25 (m, 2H), 1.72-1.85 (m, 3H), 1.32-1.43 (m, 1H); MS (CI) 403.2 ($M + \text{H}$) $^+$ 401.0 ($M - \text{H}$) $^-$; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >95%.

10 **INTERMEDIATE 25**

4-(5-Methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-3-nitro-N-phenyl-benzenesulfonamide
(Scheme 5, Method 5)

The compound was prepared from Intermediate 18 and 5-methyl-2,5-diaza-bicyclo[2.2.1]2-heptane to give 374 mg yellow solid (96%): ^1H NMR (CDCl_3 , 400 MHz) δ 8.12 (d, 1H), 7.58 (d, 1H), 7.26 (t, 2H), 7.13 (t, 1H), 7.07 (d, 2H), 6.76 (d, 1H), 4.24 (bs, 1H), 3.46-3.49 (m, 2H), 2.88 (d, 1H), 2.80 (t, 2H); 2.33 (s, 3H), 1.89 (d, 1H), 1.53 (bs, 1H); MS (CI) 389.0 ($M + \text{H}$) $^+$ 387.0 ($M - \text{H}$) $^-$; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >95%.

20 **INTERMEDIATE 26**

4-(trans-2,5-Dimethyl-piperazin-1-yl)-N-(2-methoxyphenyl)-3-nitro-benzenesulfonamide (Scheme 5, Method 5)

The compound was prepared from Intermediate 17 and 4-(trans-2,5-dimethyl-piperazine to give 409 mg of yellow solid resulted (97%): ^1H NMR (CDCl_3 , 400 MHz) δ 7.94 (d, 1H), 7.76 (dd, 1H), 7.50 (dd, 1H), 7.28 (d, 1H), 7.10 (t, 1H), 6.93 (t, 1H), 6.73 (d, 1H), 2.93-3.08 (m, 4H), 2.60 (dd, 1H), 2.31 (dd, 1H), 1.01 (d, 3H), 0.73 (d, 3H); MS (CI) 420.8 ($M + \text{H}$) $^+$ 418.8 ($M - \text{H}$) $^-$; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >95%.

30 **General procedure for reduction of the amino groups (Scheme 5, Method 5)**

Solutions of the nitro compounds (0.25 mmol) in THF (10 mL) and methanol (2 mL) were treated with Raney-Ni (100 mg) and hydrazine monohydrate (120 μ L, 2.5 mmol). After stirring at room temperature for 7 h, the suspensions were filtered through celite and washed with ethyl acetate and ethanol. Evaporation with HCl in ether gave the products. Some of the 5 products were without impurities, others had to be purified with HPLC ((YMC combiprep ODS-AQ, 50x20mm I.D.).

EXAMPLE 101

10 **3-Amino-N-(2-methoxyphenyl)-4-(3-methyl-piperazin-1-yl)-benzenesulfonamide (Scheme 5, Method 5)**

The compound was prepared from *N*-(2-methoxyphenyl)-4-(3-methylpiperazin-1-yl)-3-nitro-benzenesulfonamide to give 90 mg of the title compound (96%). 1 H NMR (CDCl₃) δ 7.44 (d, 1H), 7.11 (d, 1H), 7.10 (d, 1H), 6.97 (t, 1H), 6.85 (d, 1H), 6.84 (t, 1H), 6.72 (d, 1H), 3.97 (bs, 2H), 3.62 (s, 3H), 2.91-3.06 (m, 5H), 2.56 (t, 1H), 2.23 (t, 1H), 1.41 (s, 1H), 1.05 (d, 3H). The sulfonamide protons were not observed. 13 C NMR (CDCl₃) δ 149.4, 143.1, 141.4, 134.6, 125.4, 124.4, 121.0, 120.4, 119.2, 117.7, 113.2, 110.5, 55.6, 51.1, 50.8, 46.3, 30.3, 19.6. MS (CI neg) 375 (M-H⁺), (CI pos) 377 (M+H⁺).

20 **EXAMPLE 102**

3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-(2-methoxyphenyl)-benzenesulfonamide (Scheme 5, Method 5)

The compound was prepared from 4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-*N*-(2-methoxyphenyl)-3-nitrobenzenesulfonamide to give 97 mg of the title compound (96%). 1 H NMR (CDCl₃) δ 7.44 (d, 1H), 7.12 (d, 1H), 7.11 (d, 1H), 6.97 (t, 1H), 6.90 (d, 1H), 6.84 (t, 1H), 6.72 (d, 1H), 3.96 (bs, 2H), 3.62 (s, 3H), 3.19 (d, 1H), 3.09 (app t, 3H), 2.76 (t, 1H), 2.45 (t, 1H), 2.31-2.38 (m, 1H), 2.10-2.21 (m, 2H), 1.72-1.87 (m, 3H), 1.21 (t, 1H). The sulfonamide protons were not observed. 13 C NMR (CDCl₃) δ 149.4, 143.1, 141.4, 134.4, 125.4, 124.7, 121.0, 120.5, 119.5, 117.7, 113.2, 110.5, 55.6, 55.0, 53.3, 52.0, 49.7, 30.3, 27.3, 21.2. MS (CI neg) 401 (M-H⁺).

EXAMPLE 103

3-Amino-N-phenyl-4-piperazin-1-yl-benzenesulfonamide hydrochloride (Scheme 5,**5 Method 5)**

The compound was prepared from N-phenyl-4-piperazin-1-yl-3-nitro benzenesulfonamide to give 15 mg yellow solid (18%): ^1H NMR (MeOD, 400 MHz) δ 7.57-7.61 (m, 2H), 7.40 (d, 1H), 7.23 (t, 2H), 7.13 (d, 2H), 7.07 (t, 1H), 3.45 (t, 4H), 3.20 (t, 4H); MS (CI) 333.0 ($\text{M} + \text{H}$) $^+$ 331.4 ($\text{M} - \text{H}$) $^-$; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 96%.

10

EXAMPLE 104

3-Amino-4-(3-methyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride (Scheme 5, Method 5)

15 The compound was prepared from 4-(3-methyl-piperazin-1-yl)-N-3-nitrophenyl-benzenesulfonamide to give 33 mg white solid (35%): ^1H NMR (MeOD, 400 MHz) δ 7.57-7.62 (m, 2H), 7.35-7.41 (m, 1H), 7.12 (t, 2H), 7.02 (d, 2H), 6.97 (t, 1H), 3.53-3.58 (m, 1H), 3.31-3.40 (m, 2H), 3.16 (t, 2H), 2.99-3.05 (m, 1H), 2.79 (t, 1H), 1.27 (d, 3H); MS (CI) 346.8 ($\text{M} + \text{H}$) $^+$ 345.4 ($\text{M} - \text{H}$) $^-$; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 100%.

20

EXAMPLE 105

3-Amino-4-(4-ethyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride (Scheme 5, Method 5)

25 The compound was prepared from 3-Amino-4-(4-ethyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide to give 32 mg white solid (33%): ^1H NMR (MeOD, 400 MHz) δ 7.52-7.57 (m, 2H), 7.36 (d, 1H), 7.12 (t, 2H), 7.01 (d, 2H), 6.96 (t, 1H), 3.56 (d, 2H), 3.26 (t, 2H), 3.17-3.23 (m, 4H), 3.09 (t, 2H), 1.31 (t, 3H); MS (CI) 361.0 ($\text{M} + \text{H}$) $^+$ 359.4 ($\text{M} - \text{H}$) $^-$; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 96%.

30

EXAMPLE 106

3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-phenyl-benzenesulfonamide hydrochloride (Scheme 5, Method 5)

5 The compound was prepared from 4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-phenyl-3-nitro-benzenesulfonamide to give 50 mg white solid (49%): ^1H NMR (MeOD, 400 MHz) δ 7.63-7.69 (m, 2H), 7.47-7.52 (m, 1H), 7.23 (t, 2H), 7.13 (d, 2H), 7.08 (t, 1H), 3.08-3.78 (m, 8H), 2.12-2.35 (m, 4H), 1.79-1.88 (m, 1H); MS (CI) 372.8 ($M + H$) $^+$ 371.4 ($M - H$) $^-$; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 100%.

10

EXAMPLE 107

3-Amino-4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-N-phenyl-benzenesulfonamide hydrochloride (Scheme 5, Method 5)

15 The compound was prepared from 4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-N-phenyl-3-nitrobenzenesulfonamide to give 40 mg red solid (40%): ^1H NMR (MeOD, 400 MHz, major conformer at 300 K) δ 7.49-7.56 (m, 2H), 7.09-7.15 (m, 3H), 6.99-7.05 (m, 2H), 6.95 (t, 1H), 4.39 (bs, 1H), 4.30 (bs, 1H), 3.89 (d, 1H), 3.56 (bs, 2H), 3.09 (d, 1H), 2.88 (s, 3H), 2.34 (d, 1H), 2.20 (d, 1H); MS (CI) 359.0 ($M + H$) $^+$ 357.4 ($M - H$) $^-$; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 93%.

EXAMPLE 108

3-Amino-4-(trans-2,5-dimethyl-piperazin-1-yl)-N-(2-methoxy-phenyl)-benzenesulfonamide hydrochloride (Scheme 5, Method 5)

25 The compound was prepared from 4-(trans-2,5-dimethyl-piperazin-1-yl)-N-(2-methoxy-phenyl)-3-nitrobenzenesulfonamide to give 60 mg white solid (61%): ^1H NMR (MeOD, 400 MHz) δ 7.54-7.58 (m, 2H), 7.45 (d, 1H), 7.32 (d, 1H), 7.02 (t, 1H), 6.81 (d, 1H), 6.76 (t, 1H), 3.54-3.57 (m, 1H), 3.47 (s, 3H), 3.37 (d, 1H), 3.30-3.34 (m, 1H), 3.01 (t, 2H), 2.71 (t, 1H), 1.23 (d, 3H), 0.77 (d, 3H); MS (CI) 390.8 ($M + H$) $^+$ 389.4 ($M - H$) $^-$; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 96%.

EXAMPLE 112

5 **4-[4-(3,4-Dihydro-2H-quinoline-1-sulfonyl)-2-amino-phenyl]-[1,4]diazepane
ditrifluoroacetic acid (Scheme 5, Method 5)**

The compound was prepared from 1,2,3,4-tetrahydro-quinoline 4-chloro-3-nitro-benzenesulfonyl chloride and [1,4]diazepane-1-carboxylic acid tert-butyl ester (430 μ l, 2.2 mmol) to give (63%) as a solid. 1 H NMR (CD₃OD) δ 7.69-7.62 (m, 1H), 7.16-6.98 (m, 5H), 6.94-6.89 (m, 1H), 3.78-3.71 (m, 2H), 3.46-3.27 (m, 6H), 3.13-3.06 (m, 2H), 2.48-2.40 (m, 2H), 2.16-2.05 (m, 2H), 1.69-1.58 (m, 2H); MS *m/z* (M+1) 387.

EXAMPLE 109

15 **2-(3-Amino-4-[1,4]diazepan-1-yl-benzenesulfonyl)-benzamide diacetic acid (Scheme 5,
Method 5)**

The compound was prepared from 2-amino-benzamide, 4-chloro-3-nitro-benzenesulfonyl chloride and 1,4]diazepane-1-carboxylic acid tert-butyl to give (1%) as an oil. 1 H NMR (CD₃OD) δ 7.68-7.57 (m, 2H), 7.43-7.36 (m, 1H), 7.17-7.15 (m, 1H), 7.10-7.02 (m, 3H), 3.44-3.25 (m, 6H), 3.12-3.05 (m, 2H), 2.14-2.02 (m, 2H); MS *m/z* (M+1) 390.

20
EXAMPLE 111

**2-[1,4]Diazepan-1-yl-5-(3,4-dihydro-1H-isoquinoline-2-sulfonyl)-aniline
dihydrochloride (Scheme 5, Method 5)**

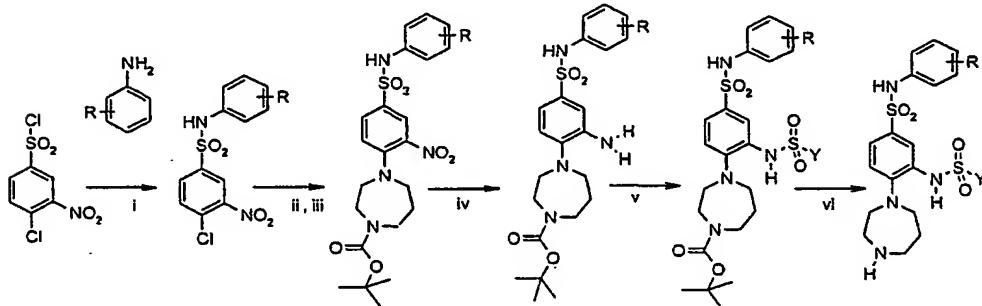
25 The compound was prepared from 1,2,3,4-tetrahydro-isoquinoline, 4-chloro-3-nitro-benzenesulfonyl chloride and 1,4]diazepane-1-carboxylic acid tert-butyl ester to give (93%) as a white solid. 1 H NMR (DMSO) δ 9.28 (s, 2 H), 7.12 (m, 7 H), 4.12 (s, 2 H), 3.20 (m, 8 H), 3.02 (t, *J* = 5.81 Hz, 2 H), 2.86 (t, *J* = 6.07 Hz, 2 H), 2.00 (m, 2 H); MS *m/z* 387 (M+1).

30 EXAMPLE 110

**4-[4-(3-Fluoro-2-methoxy-phenylsulfamoyl)-2-amino-phenyl]-[1,4]diazepane
ditrifluoroacetic acid (Scheme 5, Method 5)**

The compound was prepared from 3-fluoro-2-methoxyaniline, 4-chloro-3-nitrobenzenesulfonyl chloride and 1,4]diazepane-1-carboxylic acid tert-butyl ester to give (43%)
5 as a solid. ^1H NMR (DMSO) δ 9.70 (s, 1H), 8.79 (br s, 2H), 7.17-6.87 (m, 6H), 3.53 (s, 3H),
3.32-3.13 (m, 6H), 2.99-2.91 (m, 2H), 2.01-1.89 (m, 2H); MS m/z (M+1) 395.

Scheme 6, Method 6



10

Legend to Scheme 2:

i: Py, CH₂Cl₂; ii: K₂CO₃, CH₃CN, diamine (i. e. homopiperazine); iii: (BOC)₂O, THF, NaOH; iv: Raney-Ni, Hydrazine monohydrate, THF/EtOH; v: sulfonylchloride (Y-SO₂-Cl), Py, Et₃N, CH₂Cl₂; vi: HCl ether/MeOH

15

INTERMEDIATE 27

tert-Butyl- 4-[4-(anilinosulfonyl)-2-nitrophenyl]-1,4-diazepane-1-carboxylate (Scheme 6, Method 6)

20 Di-*tert*-butyl dicarbonate (0.921 g, 4.22 mmol) in THF (20.0 mL) was added to a solution of 4-(1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide (0.530 g, 1.40 mmol) and NaOH (0.140 g, 3.50 mmol) dissolved in THF:water (30 mL, 1:1). The solution was stirred at room temperature for 3 h. The mixture was neutralized with 5 N HCl and then the THF was removed under vacuum. The aqueous phase was extracted with CHCl₃ (2 x 50 mL)

and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated. Purification via flash column chromatography (SiO_2 , using $\text{CHCl}_3/\text{MeOH}/9.75:0.25$) gave a solid, which was triturated with $\text{EtOAc}/\text{pentane}$ to give 0.605 g (90%) of the pure product. ^1H NMR (DMSO-*d*6) δ 9.84 (br s, 1H), 8.01-7.98 (m, 1H), 7.70-7.65 (m, 1H), 7.32-7.28 (m, 1H), 7.26-7.20 (m, 2H), 7.13-7.08 (m, 2H), 7.07-7.02 (m, 1H), 3.61-3.48 (m, 4H), 3.39-3.33 (m, 2H), 3.23-3.15 (m, 2H), 1.85-1.76 (m, 2H), 1.18 (s, 9H); MS (posESI-FIA) m/z = 477 ($\text{M}+\text{H}^+$). *tert*-Butyl-4-[2-nitro-4-(anilinosulfonyl)phenyl]-1,4-diazepane-1-carboxylate was reduced to the final product by treatment with Raney-Ni and hydrazine monohydrate using method C to yield 0.477 g (91%) of the free base; ^1H NMR (DMSO-*d*6) δ 9.81 (s, 1H), 7.24-7.18 (m, 2H), 7.13-7.08 (m, 3H), 7.02-6.92 (m, 3H), 4.99 (m, 2H), 3.53-3.45 (m, 4H), 3.02-2.94 (m, 4H), 1.86-1.79 (m, 2H), 1.42 (9H); MS (posESI-FIA) m/z = 447 ($\text{M}+\text{H}^+$).

EXAMPLE 97

15 **4-(1,4-Diazepan-1-yl)-N-phenyl-3-[(methylsulfonyl)amino]benzenesulfonamide hydrochloride (Scheme 6, Method 6)**

A mixture of *tert*-butyl 4-[2-amino-4-(anilinosulfonyl)phenyl]-1,4-diazepane-1-carboxylate (176 mg, 0.39 mmol), methylsulfonyl chloride (0.040 mL, 0.47 mmol) and pyridine (0.285 mL, 3.51 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature overnight. The reaction mixture was quenched with NaHCO_3 aq (3 x 30 mL). The organic phase was separated, dried (MgSO_4) and filtered. The volatiles were evaporated followed by purification of the oily residue by chromatography (SiO_2 , hexane/ EtOAc 4:1) to give 110 mg of *tert*-butyl 4-{4-(anilinosulfonyl)-2-[(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (yield 58%).

25 ^1H NMR (CDCl_3) δ 7.90-7.85 (m, 1H), 7.50-7.43 (m, 1H), 7.30-7.24 (m, 2H), 7.20-7.08 (m, 4H), 6.84-6.79 (m, 1H), 3.65-3.51 (m, 4H), 3.12-3.06 (m, 1H), 3.04-2.96 (m, 6H), 2.04-1.91 (m, 2H), 1.49 (s, 3H); MS (posEI-DIP) m/z = 524 ($\text{M}+\text{H}^+$). *tert*-Butyl 4-{4-(anilinosulfonyl)-2-[(methylsulfonyl)amino]phenyl}-1,4-diazepane-1-carboxylate (0.077 g, 0.147 mmol) was dissolved in MeOH , and ether saturated with HCl gas was added. The mixture was stirred at room temperature for 4 h and then concentrated. The crude solid was dissolved in a small amount of MeOH , and ether was added. The precipitate

was collected and dried to give 30 mg of the pure product as the HCl salt (yield 48%): ^1H NMR (DMSO-d6) δ 7.72-7.70 (m, 1H), 7.46-7.42 (m, 1H), 7.25-7.20 (m, 3H), 7.14-7.09 (m, 2H), 7.03-6.99 (m, 1H), 3.45-3.15 (m, partly obscured by solvent signal, HDO, 6H), 2.96 (s, 3H), 2.02-1.95 (m, 2H); MS (posES-FIA) m/z = 425 (M+H $^+$).

5

EXAMPLE 96

4-(1,4-Diazepan-1-yl)-N-phenyl-3-[(phenylsulfonyl)amino]benzenesulfonamide hydrochloride (Scheme 6, Method 6)

10 To a solution of tert-butyl 4-[2-amino-4-(anilinosulfonyl)phenyl]-1,4-diazepane-1-carboxylate (0.268 g, 0.599 mmol), pyridine (338 μL , 4.19 mmol) and Et₃N (337 μL , 2.40 mmol), in CH₂Cl₂ (8.0 mL) was added benzenesulfonyl chloride (153 μL , 1.20 mmol) in CH₂Cl₂ (2 mL). The mixture was stirred at room temperature for 16 h. The reaction mixture was washed with saturated aqueous NaHCO₃, dried with Na₂SO₄, filtered and concentrated.

15 The crude material was dissolved in EtOH (5 mL) and KOH (0.134 g, 4.0 equiv.) was added. The reaction was stirred at room temperature for 2 days. Water (5 mL) was added to the reaction mixture and most of the EtOH was evaporated under vacuum. The water phase was extracted with CH₂Cl₂ (3x20 mL). The combined organic phases were dried with Na₂SO₄, filtered and concentrated. The crude boc-protected material was dissolved in MeOH, and

20 ether saturated with HCl gas was added. The mixture was stirred for 16 h and then concentrated to give 0.543 g of the crude product, which was purified by reversed phase preparative HPLC to give 0.153 g of the pure product as the acetic acid salt which was converted to the HCl-salt: ^1H NMR (DMSO-d6) δ 10.25 (s, 1H), 9.09 (br s, 2H), 7.68-7.58 (m, 4H), 7.54-7.48 (m, 2H), 7.46-7.42 (m, 1H), 7.23-7.16 (m, 3H), 7.05-6.28 (m, 3H), 3.35-3.15 (m, partly obscured by solvent signal HDO, 6H), 2.81-2.75 (m, 2H), 1.92-1.85 (m, 2H); MS (posES-FIA) m/z = 487 (M+H $^+$).

INTERMEDIATE 28

N-Naphthalen-1-yl-3-nitro-4-piperazin-1-yl-benzenesulfonamide, hydrochloride

4-Chloro-3-nitrobenzenesulphonyl chloride (0.992 g, 3.87 mmol) was added to a solution of naphthalen-1-ylamine (0.665 g, 4.64 mmol) and pyridine (3.1 mL, 38.7 mmol) dissolved in DCM (5 mL). The solution was stirred at room temperature for 2 days and the volatiles were evaporated. The crude mixture was dissolved in EtOAc and the organic phase was washed with 1 N HCl, dried with MgSO₄, filtered and concentrated to give 1.1 g of naphthalen-1-yl-3-nitro-4-chloro-benzenesulphonamide. Naphthalen-1-yl-3-nitro-4-chloro-benzenesulphonamide was dissolved in CH₃CN (10 mL) and piperazine (0.683 g, 7.93 mmol) was added. The mixture was stirred at 65 °C for 16 hours. The mixture was concentrated and the crude product was purified by flash chromatography on silica using DCM→DCM/MeOH (10%) + aqueous NH₃ (0.4 as eluent to give 0.531 g of the free base which was converted to its HCl-salt.

¹H NMR (DMSO-d₆) δ 10.36 (brs, 1H), 9.33 (brs, 2H), 8.12 (D, J = 2.1 Hz, 1H), 8.05-7.99 (m, 1H), 7.94-7.88 (m, 1H), 7.85-7.72 (m, 2H), 7.55-7.38 (m, 4H), 7.22-7.16 (m, 1H), 3.40-3.30 (m, obscured by solvent signal, 4H), 3.24-3.12 (m, 4H); MS (posES-FIA) m/z = 413 (M+H).

EXAMPLE 113**20 3-Amino-2-chloro-N-naphthalen-1-yl-4-piperazin-1-yl-benzenesulfonamide, hydrochloride**

To a solution of N-naphthalen-1-yl-3-nitro-4-piperazin-1-yl-benzenesulfonamide (0.4602 g, 11.2 mmol) in 40 mL of a 4:1 EtOH:THF solvent system was added Raney-Ni (~ 1.0 mL suspension in EtOH) followed by hydrazine mono-hydrate (2.80 g, 56.0 mmol). The mixture was stirred vigorously for 3 hours and then filtered through celite. The filtrate was concentrated and the crude product was triturated with MeOH/ether. The product was converted to its HCl-salt. Yield (90%) as the free base. An aliquot was purified by preparative LC/MS.

¹H NMR (DMSO-d₆) δ 9.20-8.90 (brs 2H), 8.25-8.21 (m, 1H), 7.90-7.86 (m, 1H), 7.74 (d, J = 8.48 Hz, 1H), 7.52-7.46 (m, 2H), 7.39-7.35 (m, 1H), 7.24-7.21 (m, 1H), 7.10 (d, J = 8.48

Hz, 1H), 6.91 (m, d, J = 8.48 Hz, 1H), 3.32-3.25 (m, obscured by solvent signal, 4H), 3.03-2.98 (m, 4H); MS (posES-FIA) m/z = 383.

BIOLOGICAL TESTS

5

The ability of a compound according to the invention to bind a 5-HT₆ receptor, and to be pharmaceutically useful, can be determined using *in vivo* and *in vitro* assays known in the art.

(a) 5-HT₆ Intrinsic Activity Assay

10 Antagonists to the 5-HT₆ receptor were characterized by measuring inhibition of 5-HT induced increase in cAMP in HEK 293 cells expressing the human 5-HT₆ receptor (see Boess et al. (1997) *Neuropharmacology* 36: 713-720). Briefly, HEK293/5-HT₆ cells were seeded in polylysine coated 96-well plates at a density of 25,000 / well and grown in DMEM (Dulbecco's Modified Eagle Medium) (without phenol-red) containing 5% dialyzed Foetal 15 Bovine Serum for 48 h at 37°C in a 5% CO₂ incubator. The medium was then aspirated and replaced by 0.1 ml assay medium (Hanks Balance Salt Solution containing 20 mM HEPES, 1.5 mM isobutylmethylxanthine and 1 mg/ml bovine serum albumin). After addition of test substances, 50 μ l dissolved in assay medium, the cells were incubated for 10 min at 37°C in a 5% CO₂ incubator. The medium was again aspirated and the cAMP content was determined 20 using a radioactive cAMP kit (Amersham Pharmacia Biotech, BIOTRAK RPA559). The potency of antagonists was quantified by determining the concentration that caused 50% inhibition of 5-HT (at [5-HT] = 8 times EC₅₀) evoked increase in cAMP, using the formula $K_{i,eff} = IC_{50}/(1+[5HT]/EC_{50})$.

25

The compounds in accordance with the invention have a selective affinity to 5-HT₆ receptors with K_i values between 1 nM and 5 μ M and they antagonized the 5-HT induced increase of cAMP. There is correlation between the K_i binding and the $K_{i,eff}$ efficacy. Moreover, the compounds show good selectivity (>100 fold) against 5-HT_{2a}, 5-HT_{2b}, 5-HT_{2c}, 5-HT_{1a}, 5-HT_{1b}.

30

(b) In vivo assay of reduction of food intake

For a review on serotonin and food intake, see Blundell, J.E. and Halford, J.C.G. (1998) Serotonin and Appetite Regulation. Implications for the Pharmacological Treatment of Obesity. *CNS Drugs* 9:473-495.

5

Obese (ob/ob) mouse is selected as the primary animal model for screening as this mutant mouse consumes high amounts of food resulting in a high signal to noise ratio. To further substantiate and compare efficacy data, the effect of the compounds on food consumption is also studied in wild type (C57BL/6J) mice. The amount of food consumed 10 during 15 hours of infusion of compounds is recorded.

Male mice (obese C57BL/6JBom-Lep^{ob} and lean wild-type C57B1/6JBom; Bomholtsgaard, Denmark) 8-9 weeks with an average body weight of 50 g (obese) and 25 g (lean) are used in all the studies. The animals are housed singly in cages at 23±1°C, 40-60 % 15 humidity and have free access to water and standard laboratory chow. The 12/12-h light/dark cycle is set to lights off at 5 p.m. The animals are conditioned for at least one week before start of study.

The test compounds are dissolved in solvents suitable for each specific compound 20 such as cyclodextrin, cyclodextrin/methane sulfonic acid, polyethylene glycol/methane sulfonic acid, saline. Fresh solutions are made for each study. Doses of 30, 50 and 100 mg kg⁻¹day⁻¹ are used. The purity of the test compounds is of analytical grade.

The animals are weighed at the start of the study and randomized based on body 25 weight. Alzet osmotic minipumps (Model 2001D; infusion rate 8 µl/h) are used and loaded essentially as recommended by the Alzet technical information manual (Alza Scientific Products, 1997; Teeuwes and Yam, 1976). Continuous subcutaneous infusion with 24 hours duration is used. The minipumps are either filled with different concentrations of test compounds dissolved in vehicle or with only vehicle solution and maintained in vehicle pre-warmed to 37°C (approx. 1h). The minipumps are implanted subcutaneously in the 30

neck/back region under short acting anesthesia (metofane/enflurane). This surgical procedure lasts approximately 5 min. It takes about 3 h to reach steady state delivery of the compound.

5 The weight of the food pellets are measured at 5 p.m. and at 8 p. m. for two days before (baseline) and one day after the implantation of the osmotic minipumps. The weigh-in is performed with a computer assisted Mettler Toledo PR 5002 balance. Occasional spillage is corrected for. At the end of the study the animals are killed by neck dislocation and trunk blood sampled for later analysis of plasma drug concentrations.

10 The plasma sample proteins are precipitated with methanol, centrifuged and the supernatant is transferred to HPLC vials and injected into the liquid chromatography /mass spectrometric system. The mass spectrometer is set for electrospray positive ion mode and Multiple Reaction Monitoring (MRM with the transition m/z 316 \Rightarrow 221).

15 A linear regression analysis of the standards forced through the origin is used to calculate the concentrations of the unknown samples.

Food consumption for 15 hours is measured for the three consecutive days and the percentage of basal level values is derived for each animal from the day before and after 20 treatment. The values are expressed as mean \pm SD and \pm SEM from eight animals per dose group. Statistical evaluation is performed by Kruskal-Wallis one-way ANOVA using the percent basal values. If statistical significance is reached at the level of $p < 0.05$, Mann-Whitney U-test for statistical comparison between control and treatment groups is performed.

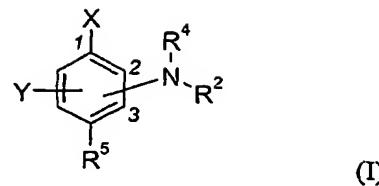
25 The compounds according to the invention show an effect in the range of 50-150 mg/kg.

TABLE VII

| EXAMPLE | Dose (mg/Kg) | Reduction of Food Intake (%) <i>po</i> administration |
|---------|--------------|--|
| 27 | 50 | 28 |
| 29 | 100 | 60 |

WHAT IS CLAIMED IS:

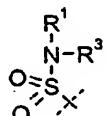
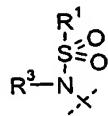
1. A compound of the formula (I)



5

or a pharmaceutically acceptable salt thereof, wherein

X is



(Ia)

(Ib)

10 R¹ and R³ are independently

- (a) H
- (b) C₁₋₆ alkyl,
- (c) C₁₋₆ alkoxy,
- (d) straight or branched C₁₋₆ hydroxyalkyl,
- 15 (e) straight or branched C₁₋₆ alkylhalides; or
- (f) a group Ar;

Ar is

- (a) phenyl,
- 20 (b) 1-naphthyl,
- (c) 2-naphthyl,
- (d) benzyl,
- (e) cinnamoyl,
- (f) a 5 to 7-membered, partially or completely saturated, heterocyclic ring containing 1 to 4
- 25 heteroatoms, selected from oxygen, nitrogen and sulfur, or

(g) a bicyclic ring system consisting of two heterocyclic rings as defined under (f), or a bicyclic ring system consisting of one benzene ring and one heterocyclic ring as defined under (f);

5 alternatively, R¹ and R³ are linked to form a group (CH₂)₂O, (CH₂)₄O, or (CH₂)₃₋₅ in formula (Ib);

optionally, the group Ar is substituted with

(a) Y, or

10 (b) a 5 to 7-membered, partially or completely saturated, heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

Y is

(a) H,

15 (b) halogen,

(c) C₁₋₆ alkyl,

(d) CF₃,

(e) hydroxy,

(f) C₁₋₆ alkoxy,

20 (g) C₁₋₄ alkenyl;

(h) phenyl;

(i) phenoxy,

(j) benzyloxy,

(k) benzoyl,

25 (l) OCF₃,

(m) CN,

(n) straight or branched C₁₋₆ hydroxyalkyl,

(o) straight or branched C₁₋₆ alkylhalides,

(p) NH₂,

30 (q) NHR⁶,

(r) NR⁶R⁷,

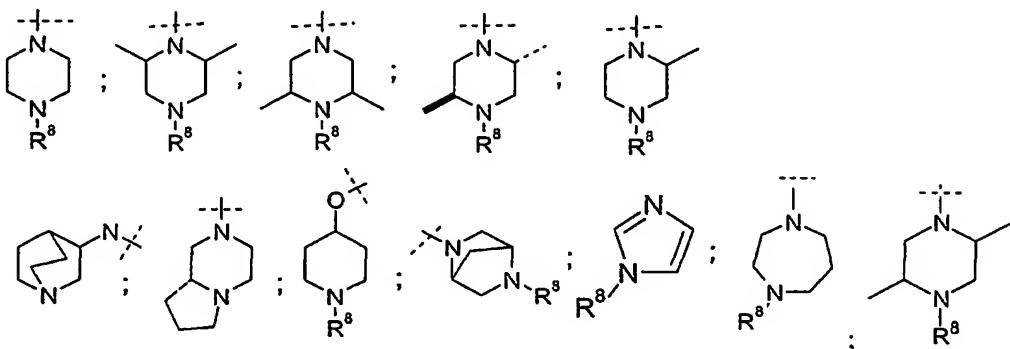
- (s) NO_2 ,
- (t) $-\text{CONR}^6\text{R}^7$,
- (u) NHSO_2R^6 ,
- (v) NR^6COR^7 ,
- 5 (x) $\text{SO}_2\text{NR}^6\text{R}^7$,
- (z) $-\text{C}(=\text{O})\text{R}^6$,
- (aa) $-\text{CO}_2\text{R}^6$, or
- (ab) $\text{S}(\text{O})_n\text{R}^6$; wherein n is 0, 1, 2 or 3;

10 R^2 and R^4 are independently:

- (a) $-\text{SO}_2\text{R}^1$,
- (b) H,
- (c) C_{1-6} alkyl,
- (d) $\text{C}_1\text{-C}_3$ alkenyl,
- 15 (e) $\text{C}_1\text{-C}_3$ alkylaryl,
- (f) Ar as defined above for R^1 ,
- (g) $-\text{C}(=\text{O})\text{R}^6$,
- (h) $-\text{C}(\text{O})\text{NR}^6\text{R}^7$,
- (i) $-\text{C}(\text{S})\text{NR}^6\text{R}^7$,
- 20 (j) $-\text{CO}_2\text{R}^6$;
- (k) $-\text{C}(\text{S})\text{R}^6$;
- (l) straight or branched C_{1-6} hydroxyalkyl, or
- (m) straight or branched C_{1-6} alkylhalides;

25 alternatively, R^2 and R^4 are linked to form a group $(\text{CH}_2)_2\text{O}$, $(\text{CH}_2)_4\text{O}$, or $(\text{CH}_2)_{3-5}$ in formula (Ia);

R^5 is selected from the group consisting of the following chemical groups:



R^6 and R^7 are independently

5 (a) H,
 (b) C_{1-6} alkyl,
 (c) C_{3-7} cycloalkyl, or
 (d) Ar, as defined above for R^1 ;

10 alternatively, R⁶ and R⁷ are linked to form a group (CH₂)₂O, (CH₂)₄O or (CH₂)₃₋₅;

R⁸ is

(a) H, or
 (b) C₁₋₆ alkyl.

15

2. A compound according to claim 1 wherein

R' is a group Ar;

20 Aris

- (a) phenyl,
- (b) 1-naphthyl,
- (c) 2-naphthyl, or

(f) a 5 to 7-membered, partially or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur;

the group Ar is substituted with Y, wherein Y is

- 5 (a) H,
- (b) halogen,
- (c) C₁₋₆ alkyl,
- (d) CF₃,
- (f) C₁₋₆ alkoxy,
- 10 (g) C₁₋₄ alkenyl;
- (h) phenyl;
- (l) OCF₃, or
- (n) straight or branched C₁₋₆ hydroxyalkyl.

15 3. A compound according to claim 1 or 2, wherein

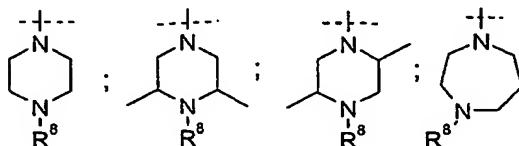
the group $\begin{array}{c} R^4 \\ | \\ -N- \\ | \\ R^2 \end{array}$ is attached to the phenyl ring in 2-position and 3-position.

4. A compound according to any one of claims 1 to 3, wherein R² is $-SO_2R^1$.

20

5. A compound according to any one of claims 1 to 4, wherein R³ and R⁴ are independently H, methyl or ethyl.

25 6. A compound according to any one of claims 1 to 5, wherein R⁵ is selected from the group consisting of the following chemical groups:



VO

wherein R⁸ is H or methyl.

7. A compound according to any one of claims 1 to 6, wherein R⁶ and R⁷ are independently
5 (a) H,
(b) C₁₋₆ alkyl,
(c) C₃₋₇ cycloalkyl, or
(d) Ar.

10 8. A compound according to claim 1, which is the compound
N-[2-{ethyl[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)phenyl]-3-
fluorobenzenesulfonamide,
N-[2-[ethyl(phenylsulfonyl)amino]-4-(4-methyl-1-piperazinyl)phenyl]
benzenesulfonamide,
15 3-fluoro-N-[2-{[(3-fluorophenyl)sulfonyl]amino}-4-(4-methyl-1-piperazinyl)
phenyl]benzenesulfonamide,
N-{5-(4-methyl-1-piperazinyl)-2-[(8-quinolinylsulfonyl)amino]phenyl}-7-
quinolinesulfonamide,
N-[2-chloro-4-({4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]anilino}
20 sulfonyl)phenyl]acetamide,
3,4-dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}
benzenesulfonamide,
3-methoxy-4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(phenylsulfonyl)amino]
phenyl}benzenesulfonamide,
25 4-methyl-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}
benzenesulfonamide,
3,4-dimethoxy-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}
benzenesulfonamide,
3-cyano-N-{4-(4-methyl-1-piperazinyl)-2-[(methylsulfonyl)amino]phenyl}
30 benzenesulfonamide,
N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide,

5-(dimethylamino)-N-{4-(1-piperazinyl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide,

N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-8-quinolinesulfonamide,

2,4,6-trimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]

5 benzenesulfonamide,

4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide,

N-[2-({[(E)-2-phenylethenyl]sulfonyl}amino)-5-(1-piperazinyl)phenyl]

benzenesulfonamide,

2,5-dimethoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]

10 benzenesulfonamide,

2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl] benzenesulfonamide,

2,4-difluoro-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]

benzenesulfonamide,

4-butoxy-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]benzenesulfonamide,

15 3,5-dimethyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]-4-oxazolesulfonamide,

5-fluoro-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]

benzenesulfonamide,

4-(methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]

20 benzenesulfonamide,

2-(methylsulfonyl)-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]

benzenesulfonamide,

2-methoxy-4-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]

benzenesulfonamide,

25 4-methoxy-2-methyl-N-[2-[(phenylsulfonyl)amino]-4-(1-piperazinyl)phenyl]

benzenesulfonamide,

N-[2-amino-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide,

N-[2-(ethylamino)-4-(1-piperazinyl)phenyl]-3-fluorobenzenesulfonamide,

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide

30 hydrochloride

N-(4-(1,4-diazepan-1-yl)-2-{[(3-fluorophenyl)sulfonyl]amino}phenyl)-3-fluorobenzenesulfonamide hydrochloride

N-{5-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-N-ethylbenzenesulfonamide hydrochloride

5 N-{5-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{5-(1,4-diazepan-1-yl)-2-[(ethylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}[1,1'-biphenyl]-4-sulfonamide

10 hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,1,3-benzoxadiazole-4-sulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride

15 N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide

20 hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

25 N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-fluorobenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-nitrobenzenesulfonamide

30 hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-(trifluoromethyl)benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride

5 N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-(trifluoromethoxy)benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-3-methoxybenzenesulfonamide hydrochloride

10 N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-4-ethylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

15 N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-3,4-dimethoxybenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[ethyl(methylsulfonyl)amino]phenyl}-7-quinolinesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

20 N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[methyl(methylsulfonyl)amino]phenyl}-5-(2-pyridinyl)-2-thiophenesulfonamide hydrochloride

25 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-(dimethylamino)-1-naphthalenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-8-quinolinesulfonamide hydrochloride

30

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,4,6-trimethylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

5 N-[5-(1,4-diazepan-1-yl)-2-({[(E)-2-phenylethenyl]sulfonyl}amino)phenyl]benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2,5-dimethoxybenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-2-methylbenzenesulfonamide hydrochloride

10 4-butoxy-N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-3,5-dimethyl-4-isoxazolesulfonamide hydrochloride

15 N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-5-fluoro-2-methylbenzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(phenylsulfonyl)amino]phenyl}-4-(methylsulfonyl)benzenesulfonamide hydrochloride

N-{4-(1,4-diazepan-1-yl)-2-[(methylsulfonyl)amino]phenyl}-N-methylbenzenesulfonamide hydrochloride

20 N-{5-(1,4-diazepan-1-yl)-2-[methyl(phenylsulfonyl)amino]phenyl}-4-methylbenzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(4-methoxyphenyl)benzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(3-methoxyphenyl)benzenesulfonamide hydrochloride

25 3-amino-4-(1,4-diazepan-1-yl)-N-(2-methoxyphenyl)benzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(3-fluorophenyl)benzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-methyl-N-phenylbenzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(4-isopropylphenyl)benzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-(4-methylphenyl)benzenesulfonamide hydrochloride

30 3-amino-4-(1,4-diazepan-1-yl)-N-(2,5-dimethylphenyl)benzenesulfonamide hydrochloride

3-amino-N-(3-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2-chlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2,4-dichlorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2-methyl-5-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

5 3-amino-N-(2-methyl-3-chloro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(4-trifluoro-phenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(4-fluorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

3-amino-N-(2-fluorophenyl)-4-(1,4-diazepan-1-yl)benzenesulfonamide hydrochloride

10 3-amino-4-(4-methyl-1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide hydrochloride

4-(1,4-diazepan-1-yl)-3-nitro-N-phenylbenzenesulfonamide hydrochloride

3-amino-4-(1,4-diazepan-1-yl)-N-phenylbenzenesulfonamide hydrochloride

2-(1,4-diazepan-1-yl)-5-(4-morpholinylsulfonyl)phenylamine hydrochloride

4-(1,4-diazepan-1-yl)-N-phenyl-3-[(phenylsulfonyl)amino]benzenesulfonamide

15 hydrochloride

4-(1,4-diazepan-1-yl)-N-phenyl-3-[(methylsulfonyl)amino]benzenesulfonamide hydrochloride

3-amino-N-(3-chlorophenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide hydrochloride

3-amino-N-(2-methoxyphenyl)-4-(4-methyl-1-piperazinyl)benzenesulfonamide

20 hydrochloride

3-amino-N-(2-methoxyphenyl)-4-(1-piperazinyl)benzenesulfonamide hydrochloride

3-amino-N-(2-methoxyphenyl)-4-(3-methyl-1-piperazinyl)benzenesulfonamide hydrochloride

3-Amino-4-(hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-*N*-(2-methoxyphenyl)-

25 benzenesulfonamide hydrochloride

3-Amino-N-phenyl-4-piperazin-1-yl-benzenesulfonamide hydrochloride

3-Amino-4-(3-methyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride

3-Amino-4-(4-ethyl-piperazin-1-yl)-N-phenyl-benzenesulfonamide hydrochloride

3-Amino-4-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-N-phenyl-benzenesulfonamide hydrochloride

3-Amino-4-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-N-phenyl-benzenesulfonamide hydrochloride

5 3-Amino-4-(trans -2,5-dimethyl-piperazin-1-yl)-N-(2methoxy-phenyl)benzenesulfonamide hydrochloride

2-(3-Amino-4-[1,4]diazepan-1-yl-benzenesulfonyl)-benzamide diacetic acid

4-[4-(3-Fluoro-2-methoxy-phenylsulfamoyl)-2-amino-phenyl]-[1,4]diazepane

ditrifluoroacetic acid

10 2-[1,4]Diazepan-1-yl-5-(3,4-dihydro-1H-isoquinoline-2-sulfonyl)-aniline dihydrochloride

4-[4-(3,4-Dihydro-2H-quinoline-1-sulfonyl)-2-amino-phenyl]-[1,4]diazepane

ditrifluoroacetic acid

3-Amino-2-chloro-N-naphthalen-1-yl-4-piperazin-1-yl-benzenesulfonamide, hydrochloride

15 9. A process for the preparation of a compound according to any one of claims 1 to 8 comprising:

(a) introduction of a cyclic diamine into halogen and nitro substituted benzene under mild and basic conditions;

(b) reduction of the nitro to the corresponding amine;

20 (c) symmetric or asymmetric sulfonylation of the amine by a sulfonylchloride;

(d) introduction of groups R³ and R⁴ by alkylation procedure in basic conditions.

10. A pharmaceutical formulation containing a compound of any one of claims 1 to 8 as an active ingredient, in combination with a pharmaceutically acceptable diluent or carrier.

25 11. A method for the treatment or prophylaxis of obesity, type II diabetes, or disorders of the central nervous system, comprising administering to a mammal in need of such treatment an effective amount of a compound of any one of claims 1 to 8.

30 12. A method for modulating 5-HT₆ receptor activity, comprising administering to a mammal in need thereof an effective amount of a compound of any one of claims 1 to 8.

13. A compound according to any one of claims 1 to 8 for use in therapy.

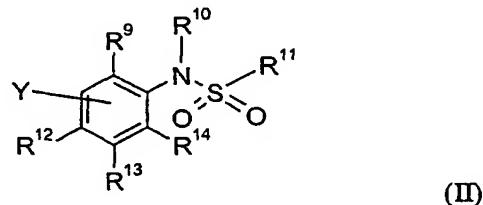
14. A compound according to any one of claims 1 to 8 for use in the treatment or prophylaxis
5 of obesity, type II diabetes, and/or disorders of the central nervous system.

15. Use of a compound according to any one of claims 1 to 8 for the manufacture of a
medicament for use in the treatment or prophylaxis of obesity, type II diabetes, and/or
disorders of the central nervous system.

10

16. A pharmaceutical formulation for use in the treatment or prophylaxis of obesity, type II
diabetes, and/or disorders of the central nervous system wherein the active ingredient is a
compound according to any one of claims 1 to 11.

15 17. A compound of the formula (II)



or a pharmaceutically acceptable salt thereof, wherein

20

R⁹, R¹² and R¹⁴ are H; or

two of R⁹, R¹² and R¹⁴ are H; and the remaining of R⁹, R¹² and R¹⁴ is

- (a) -NH₂,
- (b) -NHR⁶,
- (c) -NR⁶R⁷,
- (d) -N(CO)R⁶,
- (e) -N(CS)R⁶, or

(f) $-\text{NO}_2$;

R^{10} is a group R^3 as defined for the formula (I) in claim 1;

5 R^{11} is a group R^1 as defined for the formula (I) in claim 1;

R^{13} is

(a) homopiperazine,

(b) methylhomopiperazine, or

10 (c) a group R^5 as defined for the formula (I) in claim 1, wherein R^8 is as defined for the formula (I) in claim 1; and

Y is as defined for the formula (I) in claim 1, and

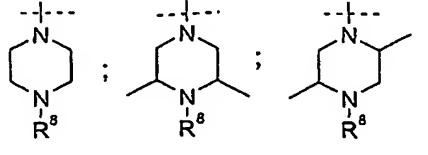
15 each of R^6 and R^7 , independently, is as defined for the formula (I) in claim 1.

18. A compound according to claim 17 wherein R^{13} is

(a) homopiperazine,

(b) methylhomopiperazine, or

20 (c) a group R^5 selected from



and

R^8 is

25 (a) H, or

(b) C_{1-6} alkyl, in particular methyl;

with the proviso that only one of R⁹, R¹² and R¹⁴ is -NH₂, -NHR⁶, -NR⁶R⁷, -N(CO)R⁶, -N(CS)R⁶, -NO₂; the other ones are H.

19. A compound according to claim 17 which is the compound

5 4-chloro-N-[5-(4-methyl-1,4-diazepan-1-yl)-2-nitrophenyl]benzenesulfonamide,
N-[2-amino-5-(1,4-diazepan-1-yl)phenyl]benzenesulfonamide,
N-[2-amino-5-(4-methyl-1,4-diazepan-1-yl)phenyl]benzenesulfonamide,
N-[4-nitro-5-(piperazinyl)phenyl]benzenesulfonamide, or
N-[4-amino-5-(piperazinyl)phenyl]benzenesulfonamide.

10

20. A process for the preparation of a compound according to any one of claims 17 to 19 comprising:

(a) introduction of a cyclic diamine into halogen and nitro substituted benzene under mild and basic conditions;
15 (b) reduction of the nitro to the corresponding amine;
(c) selective introduction of a sulfonylamide group by a sulphonylchloride reacting with the amine;
(d) introduction of a sulfonylanimo group by aromatic nucleophilic substitution.

20 21. A pharmaceutical formulation containing a compound according to any one of claims 17 to 19 as an active ingredient, in combination with a pharmaceutically acceptable diluent or carrier.

22. A method for the treatment or prophylaxis of obesity, type II diabetes, or disorders of the 25 central nervous system, comprising administering to a mammal, in need of such treatment an effective amount of a compound according to any one of claims 17 to 19.

23. A method for modulating 5-HT₆ receptor activity, comprising administering to a mammal in need thereof an effective amount of a compound according to any one of claims 17 to 19.

30

24. A compound according to any one of claims 17 to 19 for use in therapy.

25. A compound according to any one of claims 17 to 19 for use in the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system.

5 26. Use of a compound according to any one of claims 17 to 19 for the manufacture of a medicament for use in the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system.

10 27. A pharmaceutical formulation for use in the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system wherein the active ingredient is a compound according to any one of claims 17 to 19.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00906

A. CLASSIFICATION OF SUBJECT MATTER
C07D 295/04, C07D 241/04, C07D 211/46, C07D 233/56, C07D 243/08, C07D 215/36, C07D 453/02, C07D 487/04, C07D 487/08, A61K 31/495, A61K 31/551, A61K 31/4164, A61K 31/445, A61K 31/439, A61K 31/496, A61P 3/04, A61P 3/10, A61P 25/00, A61P 5/48
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, WPI DATA, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | DE 2239846 A (FARBWERKE HOECHST AG), 14 February 1974 (14.02.74) -- | 1,3,5-7 |
| X | DE 2334562 A (FARBWERKE HOECHST AG), 30 January 1975 (30.01.75) -- | 1,3,5-7 |
| X | DE 2459394 A (HOECHST AG), 24 June 1976 (24.06.76) -- | 1-3,5-7 |
| X | WO 0116094 A1 (AVENTIS PHARMA DEUTSCHLAND GMBH), 8 March 2001 (08.03.01) -- | 1-3,5-7 |

 Further documents are listed in the continuation of Box C. See patent family annex.

| | |
|---|--|
| Special categories of cited documents: | |
| "A" document defining the general state of the art which is not considered to be of particular relevance | "T" later document published after the international filing date or prior to the date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "E" earlier application or patent but published on or after the international filing date | "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" document referring to an oral disclosure, use, exhibition or other means | "&" document member of the same patent family |
| "P" document published prior to the international filing date but later than the priority date claimed | |

| | |
|--|---|
| Date of the actual completion of the international search | Date of mailing of the international search report |
| 12 August 2002 | 23 -08- 2002 |
| Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86 | Authorized officer VIVECA NORÉN/BS Telephone No. + 46 8 782 25 00 |

INTERNATIONAL SEARCH REPORT

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|--|--|
| International application No. PCT/SE 02/00906 | |
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **11-12 and 22-23**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

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Claims 11-12 and 22-23 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

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